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1820 "A CENTURY OF SERVICE" 1921

THE

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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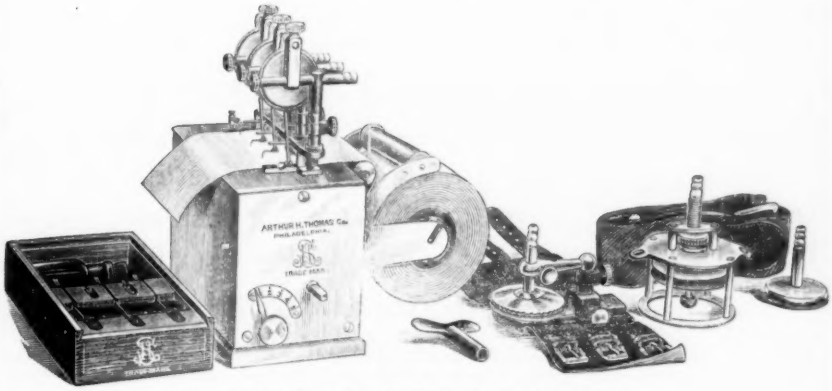

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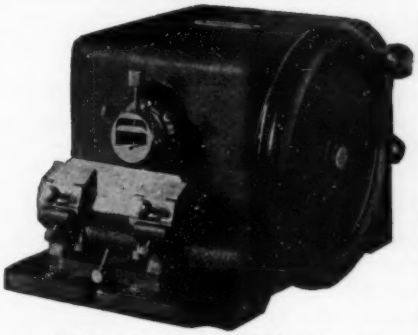

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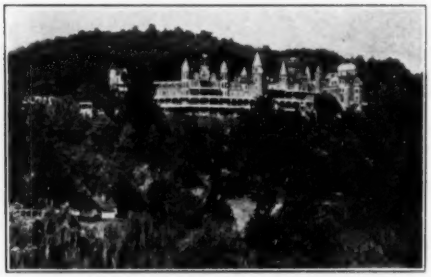

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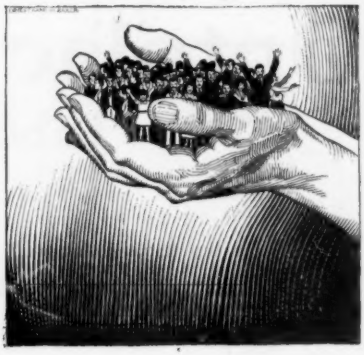

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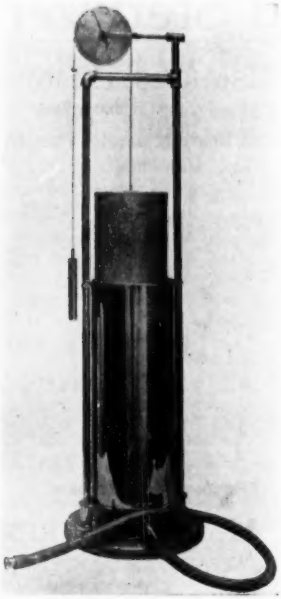

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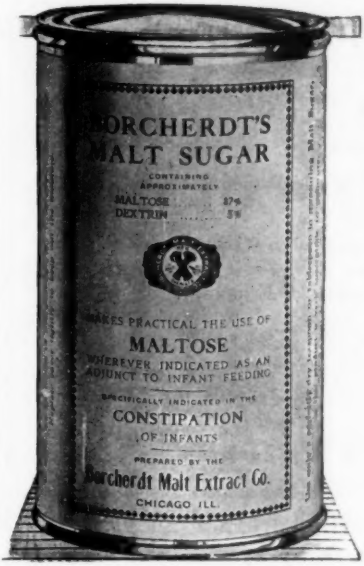

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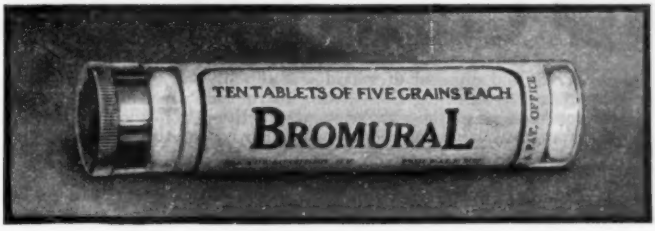

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ORIGINAL ARTICLES.

ACUTE CEREBELLAR ENCEPHALITIS (ACUTE CEREBELLAR ATAXIA).*

By J. P. Crozer Griffith, M.D.,

PROFESSOR OF PEDIATRICS IN THE UNIVERSITY OF PENNSYLVANIA.

The great interest which has been awakened in the subject of acute non-suppurative encephalitis, owing to the prevalence of an epidemic of the disorder, leads me to a further elaboration of an earlier study of this form of inflammation of the brain, particularly as it affects the cerebellum and as it is manifested in children. It has been my fortune to encounter four isolated cases in which the symptoms indicated that the cerebellum suffered very decidedly from the attack, if, indeed, it did not bear the brunt of it. These have been reported in two earlier publications,[1] together with the abstracts of all the cases I had discovered recorded in journal literature up to 1915, making twenty-one in all. In all of these the attack was acute and the affection occurred in early life.

It will not be necessary to repeat here the abstracts of the cases which I have already collected. They were of reports by Shepherd,[2] Schepers,[3] Feith,[4] Bastian,[5] Lenhartz,[6] Hammarberg,[7] Lüthje,[8]

* Read before the First Meeting of the Association for Research in Nervous and Mental Diseases, December 29, 1920.

[1] Griffith: Am. Jour. Med. Sci., 1916, **151**, 24; Am. Jour. Dis. Children, 1920, **20**, 82.

[2] Med. Times and Gaz., 1868, **1**, 144.

[3] Berl. klin. Wchnschr., 1872, **9**, 517.

[4] Allg. Ztschr. f. Psychiat., 1873–4, **30**, 236.

[5] Lancet, 1878, **2**, 207.

[6] Berl. klin. Wchnschr., 1883, **20**, 312.

[7] Nord. med. Arkiv., 1890, **22**, No. 23.

[8] Deutsch. Ztschr. f. Nervenheilk., 1902, **22**, 280.

Frederick Taylor,[9] Voelcker,[10] Guthrie,[11] Batten,[12] Nonne[13] and the four seen by myself, making a total of twenty-one cases in all. The following are abstracts of cases which have appeared in medical journal literature since the time mentioned, now about six years ago, or of the cases which were inadvertently omitted from my paper, those being selected which seem with good reason to belong to this category:

Clapton.[14] Female. Well until four years, when, after measles, was unable to walk or talk for six months. Then up to fifteen years walked unsteadily. Could not use her hands with certainty or ease and was dull mentally. Must have then gradually improved, and when married at thirty-two years could take long walks, although she had to walk slowly. With pregnancy gait became more unsteady and she was dull of comprehension, but could still attend to domestic duties. Died shortly after confinement. Autopsy showed decided atrophy of cerebellum.

NOTE. This case is very much like the one reported by Hammarberg. The onset was distinctly acute and the condition must have been an encephalitis; but many data are lacking. Recovery, although partial, had yet been very decided.

Fairbanks.[15] Child, sex not given, aged five years. Had a severe attack of measles when four and a half years old—about six months before seen—followed in two weeks by prolonged screaming, unsteady gait, staggering, ataxia of right hand. Mind clear; speech unaffected. Examination showed Romberg's symptom; staggering gait; no nystagmus; normal speech; ataxia of the right hand; right knee-jerk slightly greater than left; plantar reflex normal; Babinski reflex present. Under observation about one month (?), during which time there was decided improvement.

NOTE. The connection with measles and the acute condition seem to be undoubted, and the degree of improvement renders ultimate recovery to be hoped for.

E. S. Taylor.[16] Case 1, girl, aged ten years. Measles nine weeks before admission, followed in a week by headache. When taken from bed a week later had a nodding movement of the head backward and in four days was unable to stand and had pain in the left chest. Examination showed movements of the head when the child was in a sitting position; speech slow and hesitating; knee-jerks present; pupils normal; no nystagmus; extreme ataxia when placed on feet and apparently vertigo. Improvement remarkably rapid

[9] Lancet, 1904, **2**, 1416. [10] Brain, 1905, **28**, 360. [11] Ibid., 363.
[12] Brain, 1905, **28**, 489, 490; Clin. Soc. Tr., 1907, **11**, 276, 277.
[13] Neurolog. Centralbl., 1909, **28**, 885.
[14] Tr. Pathol. Soc. of London, 1871, **22**, 20.
[15] Arch. Pediat., 1907, **24**, 770. [16] Guy's Hospital Rep., 1913, **67**, 98.

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and seemingly complete in about twelve weeks from the onset of the measles.

E. S. Taylor. Case 2, girl, aged seven years. While in apparently perfect health fell suddenly and could not stand. Headache the next morning. Examination two days later showed speech monotonous and abrupt; child apathetic; knee-jerks present; no nystagmus; irregular movements of the head; could not sit without assistance; completely ataxic when standing and support was necessary; no vertigo; an intention-tremor of both arms; spinal fluid normal; slight fever; well-marked asynergia and adiadokokinesia. In less than three weeks no signs of cerebellar disease remained.

NOTE. Taylor emphasized the occurrence in both cases of sudden onset, extreme ataxia without loss of power and a characteristic slow, jerking speech.

Strümpell.[17] Boy, aged four and a half years. One day, about four weeks after the beginning of a moderate whooping-cough, complained that eyes did not feel so well. Better the next morning, but on the day following was taken suddenly with inability to stand and could scarcely see. This attack was not immediately preceded by any severe paroxysm. Examination four days later showed normal intelligence; dilatation of pupils; apparently a diminution of power of movement of the eyes; complete bilateral amaurosis; typical bilateral optic neuritis; no ataxia of arms; knee-jerks not obtained; well-developed ataxia of the trunk; sways greatly when placed on his feet and could not stand alone. Lumbar puncture was negative. Improvement was very rapid and complete in about six weeks.

NOTE. Strümpell describes this case as an undoubted one of ataxia of the cerebellar form, but is uncertain whether the lesion was in the cerebellum or in the corpora quadrigemina.

A. Gordon.[18] Child, aged seven and a half years, sex not stated. At five years had a very severe diphtheria followed by ataxic gait and station; increased knee-jerks; ataxia of the upper extremities; nystagmus; the child appeared dull and to understand with difficulty. Under observation for a year without improvement.

NOTE. This would appear to have been an acute encephalitis of the cerebellar type after diphtheria. Basing the opinion upon the histories of certain other cases it is possible that improvement or even recovery might yet take place.

Seham.[19] Boy, aged ten years. Condition commenced acutely with a drunken gait. During two months this grew worse; there

[17] Deutsch. Ztschr. f. Nervenheilk., 1914–15, **53**, 321.
[18] Jour. Nerv. and Ment. Dis., 1918, **47**, 370.
[19] Arch. Pediat., 1919, **36**, 531.

was trouble with writing; diplopia; slow, uncertain and scanning speech; static ataxia and support needed; nystagmus; strabismus; incoördination of hands; sensation normal; patellar reflexes increased; intelligence normal. Improvement went on slowly. In four months he could stand without difficulty, although the gait was reeling. Three and a half years later a letter states that the boy goes to school, walks alone sometimes for miles and speech is much better.

NOTE. The sudden onset points distinctly to an acute lesion, such as an encephalitis, and the existence of this condition is borne out by the almost complete recovery at the last note.

Mills and Wilson.[20] Girl, aged three years. Shortly after an attack supposed to be influenza she grew gradually more unsteady on her feet, and three months later a severe attack of indigestion and vomiting was followed by great difficulty in standing and walking and then by inability to sit upright. Examination showed cerebellar gait and station; some marked cerebellar asynergy in the upper extremities, with inability to control the motion of the hands; alternating strabismus and nystagmus. No note made of condition of speech or of psychic symptoms. Improvement steady during two weeks of observation.

NOTE. This case apparently dates from the attack of influenza, with a recurrence of the intracranial disturbance at the time of the severe attack of indigestion.

Skoog.[21] Girl, aged four years. Measles followed on the twelfth day by unsteadiness of hands and interference with walking. In a short time she could hardly get about. Examination on the third day after the onset showed the patient a little sulky or obstinate, but otherwise cerebration good; coarse tremor of tongue; slight nystagmus; no paralysis; sensation normal; deep reflexes slightly increased; all movements of extremities moderately ataxic; standing and walking difficult; all incoördination typically cerebellar in type; cerebellar asynergia evident. Improvement rapid and in seven weeks after onset of the nervous symptoms was complete.

Reh.[22] Girl, aged seven and a half years. Grippe developing on the fourth day into delirium, yet no unconsciousness, and the child could hear and obey orders given. There was very marked static ataxia, with difficulty in keeping from falling when on her feet. Apparently no other disturbance of motility; sensibility unimpaired; knee-jerks exaggerated; slight rigidity of the neck. Spinal fluid showed no noteworthy alteration. By the seventh day the delirium was replaced by moderate temporary somnolence

[20] Arch. Neurol. and Psych., 1919, **1**, 567.
[21] Jour. Am. Med. Assn., 1920, **74**, 1697.
[22] Arch. d. méd. des enf., 1920, **23**, 362.

and the fever had ceased, By the ninth day the ataxia had disappeared. By the thirteenth day there was some sciatic pain. The patient was out of bed, apparently well, in a month.

It has not been possible to make a search for cases clearly belonging to the present epidemic of encephalitis and which have been reported and are to be classified as perhaps constituting a cerebellar form of this disease. A number of such have been described in adults, as, for instance, by Redlich,[23] and seen in soldiers in whom ataxia of a cerebellar type was present; but I have not read of any in children, although in the vast literature of the present epidemic there are doubtless such on record. There have repeatedly been described during the epidemic instances of a myoclonic form of encephalitis which to a slight degree suggests the tremor seen in some of the reported instances of cerebellar ataxia, but without exhibiting any true ataxia or other symptoms which would form this complex. I have myself seen at least three instances of this condition in children. As already indicated a number of cases have also been described of a choreiform or choreo-ataxic or choreo-athetotic encephalitis, in some of which the movements appear to hold a mid-situation between those of chorea and ataxia. Such cases in children have been reported, for instance, by Roge,[24] Stertz,[25] Zimitz,[26] Massary,[27] R. C. Hamill[28] and others, and one or two have come under my own observation; and Economo[29] in discussing such cases expressed the view that the lesions are especially in the tissues leading from the cerebellum to the thalamus. Cases of this sort, although approaching in symptoms those described in this communication, exhibit other features distinguishing them. All go to support the accepted view that the lesions of encephalitis, epidemic or otherwise, are by no means confined to any one region and that borderline cases must of necessity occur.

It is difficult to give any synoptical account of the onset and course of the disease, since these vary so greatly. The description of an imaginary typical case would read somewhat as follows: The onset is acute, with unconsciousness and absence of speech, these possibly being preceded by initial vomiting or convulsions. The unconsciousness disappears in a few days, yet with this occurrence it is noted that the mentality is not quite normal; that the returning speech is affected in various ways, suggesting difficulty in enunciation rather than in thought; that there is a very decided degree of ataxia of the limbs, and often of the head and trunk; and that the patient cannot walk at all or only with a staggering gait.

[23] Ztschr. f. d. ges. Neurol. u. Psychiat., 1917, **37**, 1.
[24] Bull. et mém. de la Soc. méd. des hôp., 1920, **36**, 246.
[25] München. med. Wchnschr., 1920, **67**, 225.
[26] Wien. med. Wchnschr., 1920, **70**, 474.
[27] Ibid., 542.
[28] Arch. Neurol. and Psych., 1920, **4**, 44.
[29] Wien. med. Wchnschr., 1920, **70**, 475.

Convalescence progresses more or less slowly; less often rapidly, the mentality usually soon becoming normal, the ataxia and disturbance of speech disappearing more gradually, and the case recovering in many instances with little if any trace of the disorder remaining; often, however, with evidences of permanent damage, especially of a psychic nature.

The great variation in symptoms spoken of makes it necessary to review some of them more in detail: Some disturbance of the sensorium has been observed in the majority of the cases. This is often transitory, sometimes long continued, and is of a varied nature. Unconsciousness is comparatively common. It was stated to have been present in 12 of the 31 cases. It is usually of brief duration, but sometimes prolonged, in one instance lasting as long as seven weeks (case of Lüthje). Although it was seen in only the fourth of my personal cases, in this it lasted, with entire immobility, four or five days, and after that a soporose state continued for a decidedly longer time, the condition very strongly suggesting the four instances of epidemic stupor reported by Batten and Still.[30] Convulsions have been reported in but three or possibly four cases. In my fourth case frequently repeated convulsions continued during the first sixty hours.

Vomiting is not common. It was observed in 8 cases, but was only occasional and insignificant. Pain of any sort, oftenest in the head, is distinctly uncommon. It was recorded in only 6 of the 31 cases. Among disturbances of mentality observed other than unconsciousness may be mentioned a lethargic or dazed condition; apathy; delirium; violent and prolonged screaming; a state of fear; a maniacal state; and a diminution of intelligence. Some such affection of mentality was present in 19 of the 31 cases. This has been of variable duration. One of the shortest, in those in which the psyche was affected at all, was in the first patient under my own care, in whom attacks of screaming and a dazed or dull condition of the intellect lasted for more than a week. In some of the cases the continuance has been several months and in not a few others it was still present after several years in the form of mental backwardness and gave promise of being permanent.

Speech was reported affected in 22 of the 31 instances, and I refer only to the condition after any unconsciousness which might have been present had disappeared. In many instances there was for a time entire inability to speak. Later, after the power of speech began to return, utterance remained still far from normal, being described as drawling, or slow, or jerking, or irregular in some way, according to the case. In at least 9 cases speech was entirely absent for a time; and although the continuance of this state was usually brief, sometimes it was decidedly prolonged. Periods of

[30] Lancet, 1918, **1**, 636.

one and a half, three, five and six months are on record. One of my own cases did not speak at all for five months. So great a duration of absolute absence of speech is unusual; but, on the other hand, the recovery of perfect speech is generally distinctly delayed. In one of my cases speech had become entirely distinct within seventeen days from the onset while in one of the collected cases it was still abnormal a year after the attack. Other cases give likewise a duration very variable in time. Even as much as three and a half years after the attack the speech was still affected in one case, that of Frederick Taylor, which finally recovered entirely. The slowness with which all speech-defect disappears is shown by the fact that in only 10 of the 22 cases who had disturbance of speech is it indicated that the recovery of it was complete. In the remainder the patients passed from observation with the defect still present to some extent, although in many of these there was nothing but a slight hesitation or slowness remaining. There seems no doubt that in some of the more persistent instances of delay in recovery the trouble was to be assigned, at least in part, to the continuance of a disturbed mental state, and this statement perhaps applies as well to the early entire disappearance of the power of speech; but in the greater number of cases the defects of utterance were of a nature clearly dependent upon incoördination.

A very prominent symptom was ataxia, present in all the cases. It was sometimes slight, and then of later appearance and entirely of less importance than were the cerebral symptoms. In nearly all, however, it has been a very early and prominent manifestation. It affected most frequently the legs, interfering with standing or producing a drunken cerebellar gait. Nearly always the arms were involved as well, and sometimes the head and the trunk. A rhythmic nodding of the head, which might be classed as a manifestation of static ataxia, is recorded in six instances. The degree of ataxia was variable. In some cases it entirely interfered for a considerable time with standing or walking, even as long as twenty-two months in one instance (Frederick Taylor). Generally in the course of a few weeks the power to walk was regained, although with a gait which was decidedly incoördinate. The duration and course of the ataxia progressed to a large degree *pari passu* with the disturbance of speech. In the mildest cases all evidence of it had disappeared within three weeks.

Other symptoms which have been described are less constantly present. In some of the cases in which tremor is mentioned it is doubtful whether this may not have been a manifestation in reality of ataxia. Whatever its indication it has not been seen frequently—in only 6 of the 31 cases in all. Nystagmus was peculiarly marked in 2 of my own cases and absent in 2. Taking all the 31 reported cases as a group, nystagmus was observed in 10 instances. Strabismus was seen in 5 or possibly 6 instances. Optic neuritis was found

in but 2 cases. Loss of sphincter control was observed in 3. "Loss of power" or "paresis" has been reported in a number of instances. It was not present in the sense of paralysis in 3 of my 4 cases, and in the remaining 1 was no more than hypotonia lasting during the comatose phase of the attack. It is extremely likely that in nearly all instances which have been observed it is in reality a loss of control, not of power. The reflexes as represented by the knee-jerks are active or normal so far as any reports have been made on the subject by the writers. This was the condition mentioned in 17 instances. Ankle-clonus has occasionally been found—4 cases in all. Vertigo or dizziness has, as a rule, not been reported. It was complained of slightly in 2 of my own cases, but there has been mention of its presence in but 1 other. Still, with the presence of ataxia in every case and with the youth of the patient precluding any very accurate description by him, it is difficult to determine just what influence vertigo may have had in the production of the staggering gait. It is reasonable to conclude that, apart from the ataxia, vertigo may have shared in the action in some instances. Disturbance of sensibility has been rarely reported, anesthesia being mentioned only once.

The age of the 31 patients ranged from three to twelve years, 18 of them being six or more years old. The immediate causes of the disease without reference here to the actual nature of the affection itself have been varied. The occurrence of some infectious disorder appeared to have been the precursor in 24 of the 31 cases, measles immediately preceding in 8, influenza in 5 and typhoid fever in 4. It is interesting to note that 3 of the typhoid fever cases occurred in children of one family (Lüthje). In all of the 24 cases the encephalitis immediately followed upon or developed during the infectious disease. In 1 case dysentery was the precursor, and this might perhaps with reason be included among the cases of infection. In another case the attack was preceded by trauma of the head, but just what the etiological relationship may have been is uncertain. In 4 instances there had been no previous illness observed. As to the sex, 17 of the patients were females and 12 males and in 2 no statement is made.

The nature of the affection is naturally of the greatest interest. There appears to be no question that it is an encephalitis, and also that it is a process not limited to any one portion of the brain. Symptoms other than those supposedly cerebellar have been seen in practically every case referred to in this report. Fever, unconsciousness, delirium, convulsions and the like, which may occur, certainly cannot be called cerebellar symptoms, nor can the various later alterations of the mentality. After the unconsciousness passes away the presence of the cerebellar symptoms becomes manifest. The absence of speech, at first probably cerebral, is replaced later by various affections of utterance, which indicate in most instances,

as I have said, rather a lack of control, although mental defect may have had some influence in others.

The possible relationship of the disease to the epidemic encephalitis which is now so prominently before our attention is of great interest. With an increasing knowledge of the numerous types of this latter disorder it would appear very probable, as I have already stated, that in many instances of this cerebellar symptoms are naturally to be expected. As a matter of fact we do know that the lesions of lethargic encephalitis, which affect predominatingly the gray matter at the base of the cerebrum, may involve also the cerebellum or other regions. So far as the cases now under consideration are concerned it must be said that they have occurred for the most part independently of any epidemic, in connection with various other possible causes, and cannot be attributed to an encephalitis of any specific microbic nature.

We know little regarding the actual lesions which were present in any of the 31 cases, for the reason that only 2 of them came to autopsy, and that this was years later, death being preceded by symptoms of mental failure. The prognosis, therefore, as to survival is good, but that of complete recovery is far more uncertain. In my first case recovery was complete in one month, while in one of the cases observed by E. S. Taylor the child was well in three weeks. Complete recovery in less than six months was reported in 8 instances and nearly complete recovery in less than one year in 3. The case reported by Frederick Taylor still showed symptoms three and a half years after the onset, but none when an examination was made twenty years after the attack. It is evident, therefore, that we must be guarded before making a decision that progress toward recovery has fully ceased. A total duration of three or four months might perhaps be assumed as an average for the more acute symptoms, but this is only an approximation. In about one-third recovery was absolutely complete when the patient was last seen, while in some others it was almost entirely so when the last note was made, and in still others we may fairly assume that complete recovery soon took place. In quite a number of instances, however, we are in doubt as to the final disappearance of symptoms, and in certain of these the symptoms might be expected to persist for certainly a long time, and perhaps even permanently. The disquieting element is that in about one-quarter of the cases there was at the last observation some evidence of mental defect.

CLINICAL STUDIES IN FUNCTIONAL DISTURBANCES.

STUDY I. FUNCTIONAL THYROID TESTS AS AN AID TO DIFFERENTIAL DIAGNOSIS.*

By Nelson G. Russell, M.D., John A. P. Millet, M.D.,
and
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Introduction. During the past few years a great deal of interest has been centered upon the use of various functional tests as aids to the clinician in the diagnosis of suspected thyroid disease and as a measure of the degree of thyroid activity where a functional disturbance of this gland has been recognized to exist. The tests of thyroid function which have found widest application are the estimations of the basal metabolic rate, the glucose tolerance and the adrenalin sensitivity.

Our purpose in offering the ensuing study was to correlate these three tests in disturbances of the thyroid and to note the results of their use in other endocrinopathies and various conditions of chronic disease. Heretofore no study based on the joint application of all these tests has been made, although there have been many published in which one or two have been used.

While it is not the purpose of this paper to present a complete bibliography, it is not perhaps amiss to recall some of the more important contributions to this subject.

Bibliography. Basal Metabolism. It has become a generally accepted teaching, as a result of the extended researches of numerous competent workers, that the basal metabolic rate is a reliable index of the degree of thyroid activity. Thus, Means[1] states in a recent publication: "So characteristic of thyroid disease are changes in the basal metabolism that, personally, I believe that in the metabolism level we have a functional test of that gland, increase meaning hyperthyroidism and decrease meaning hypothyroidism, provided, of course, that other diseases that alter basal metabolism are excluded." The above sentence summarizes well the feeling of numerous others who have made use of this test. DuBois,[2] Boothby,[3] McCaskey[4] and Sandiford[5] have all subscribed to the same view. Peabody, Wearn and Tompkins[6] are of the opinion that a normal metabolic rate is sufficient evidence in itself to eliminate a previous diagnosis of hyperthyroidism.

* Read before the American Climatological and Clinical Association, June, 1920.

GLUCOSE TOLERANCE. A vast amount of work has been carried out in recent years on the utilization of glucose in various conditions, and it is the opinion of most workers that alimentary hyperglycemia occurs in almost every case of hyperthyroidism. Hamman and Hirschman,[7] Denis and Aub,[8] Janney,[9] McCaskey[10] and Lueders[11] are among those who have contributed toward forming this conclusion.

ADRENALIN SENSITIVITY. Numerous observations, alike of clinicians and physiologists, lend support to the view that the active principle of the thyroid sensitizes the sympathetic nerve-endings to the action of adrenalin. Foremost among the American workers in this field are Goetsch,[12] Barker and Sladen,[13] Cannon and Cattell[14] and Levy.[15 16] A good working bibliography and a brief theoretical discussion are presented in Goetsch's paper. Since the appearance of his work the adrenalin sensitivity test has been widely used in this country, though the conclusions reached as to its diagnostic significance have not always agreed with those of Goetsch himself. In this country Peabody and his associates showed that 60 per cent of cases of "irritable heart" in soldiers reacted positively to adrenalin.[17] They confirmed Goetsch's statement that normal subjects are not sensitive to the dosage employed (0.5 c.c. of 0.001 solution of adrenalin chloride or its equivalent in the solid form). The normals studied by Peabody and his associates were soldiers in training. O'Hare[18] showed that cases of hypertension exhibit a definite hypersensitiveness to adrenalin, although the type of response is not identical with that obtained by Goetsch and others in cases of hyperthyroidism. Boothby and Sandiford[19] find that there is no relationship between the character of the adrenalin reaction and the degree of thyroid activity. Woodbury[20] alone thinks that there are certain cases of thyrotoxicosis, dependent upon toxic adenomata, which, while showing hypersensitiveness to adrenalin, may present no increase in the basal metabolic rate. His ideas are identical with those of Goetsch,[21] though the latter did not make any estimations of the basal metabolism in the cases which he reported. A few foreign writers have made contributions to the subject, notably Ramon Turro,[22] Bernard[23] and Troell,[24] whose ideas are strikingly similar to those of Goetsch and Woodbury.

Methods. In order to secure a clinical impression independent of the results of the functional tests a complete history was taken of every case and a careful physical examination recorded. In all cases the blood-urea nitrogen was determined, and in most cases blood counts, urinalyses and Wassermann tests on the blood serum were carried out.

BASAL METABOLISM. The portable respiration apparatus devised by Benedict[25 26] was used in making all the determinations recorded in this paper. The calculation of the basal metabolic rate was based entirely on the oxygen consumption. The standard method of

determining surface area was employed as outlined by DuBois,[27] while the standards of sex and age were taken from *Clinical Calorimeter*, Study XXX.[28] We had the opportunity of controlling this method with others in two instances in which the variation proved to be less than 5 per cent, a fact which makes us feel that this method in our hands was sufficiently accurate for clinical purposes. Furthermore, the results obtained conformed very well to the clinical impression of the cases and were borne out by their subsequent progress. The operation of the apparatus, while not tedious or complicated, offers a few technical difficulties which must be constantly borne in mind in order to secure accurate and uniform results.

GLUCOSE TOLERANCE. A slight modification of the technic employed by Janney was used for the determination of the glucose tolerance. Samples of blood and urine were taken on a fasting stomach. The patient was then given an amount of glucose corresponding to 1.75 grams per kilo of body weight. This was administered orally in a 40 per cent aqueous solution flavored with the juice of a lemon, which was prepared the night before and kept in the ice-box. The blood sugar was determined on the fasting specimen and again two hours after the administration, and the urine tested for sugar hourly over a period of four hours. The blood sugar was determined by Myers's[29] modification of the Lewis and Benedict method. For the purpose of describing in a roughly quantitative fashion the degree of intolerance exhibited to glucose we have made use of the following arbitrary scale:

Plus minus (±), a reaction of doubtful significance.

1. Two-hour blood sugar more than 150 mgm. and less than 200 per 100 c.c. of blood—no glycosuria.

2. Two-hour blood sugar less than 150 mgm. with glycosuria (trace) in one specimen.

One plus (+), a slightly positiye reaction.

1. Two-hour blood sugar less than 150 mgm. with definite glycosuria in more than one specimen (traces, not complete reduction).

2. Two-hour blood sugar more than 200 mgm. without glycosuria.

Two plus (++), a moderately positive reaction. Two-hour blood sugar less than 200 mgm. with glycosuria (complete reduction) in more than one specimen.

Three plus (+++), a strongly positive reaction. Two-hour blood sugar more than 200 mgm., with complete reduction in more than one specimen.

ADRENALIN SENSITIVITY. The sensitivity of all patients to adrenalin was determined by the subcutaneous injection of 0.5 c.c. of a 1:1000 solution of adrenalin chloride (Parke, Davis & Co.), the effect on pulse and blood-pressure being noted, and observations taken on the subjective and objective response in accordance with the technic recommended by Goetsch.[12] While no physiological tests were made to assay the strength of the solutions used, the frequency of positive responses was considered sufficient proof of

their activity. During the later tests a rest period of at least one-half hour was employed, in order to bring the pulse and blood-pressure to a steady base line and to observe the effect of a subcutaneous injection of 0.5 c.c. sterile water. All the tests in this series except

INITIALS	SERIES NUMBER	LAB. NUMBER	AGE	SEX	BASAL METABOLIC RATE: BUCCAL TEMPERATURE	WEIGHT	CALORIES	METABOLISM	GLUCOSE TOLERANCE TEST: BLOOD: FASTING	2 HOURS	URINE: FASTING	1 HOUR	2 HOURS	3 HOURS	4 HOURS	INTERPRETATION	ADRENALIN SENSITIVITY TEST: BLOOD PRESSURE: SYSTOLIC	DIASTOLIC	PULSE	RESPIRATION	OBJECTIVE	SUBJECTIVE	INTERPRETATION	REMARKS
CF	1	117	54	♀	98.8	44.0	1147	+13	160	160	0	C R	Tr	Tr	0	++	170/	150/	96/	-	-	ND	Exoph. Goitre (Case also Thyroidectomy)
GP	2	121	21	♀	98.8	61.0	1380	+52	110	170	0	Tr	Tr	0	0	++	115/ 140	105/ 110	120/ 108	23/ 17	++	++	++	Exoph. Goitre (Case Lipiodol Op.
GD	3	132	40	♀	97.4	40.0	1158	+28	100	120	0	0	0	0	0	0	125/ 145	95/ 95	96/ 96	24/ 28	+	++	++	V	Thyroid Hyperplasia
HD	4	133	21	♀	98.0	50.0	1280	+32	90	90	0	0	0	0	0	0	135/ 155	82/ 105	108/ 108	25/ 28	+	+	+	+	Exoph. Goitre
LR	5	135	49	♀	98.6	51.2	1696	+92	130	140	0	0	Tr	Tr	0	+	130/ 150	90/ 90	112/ 108	30/ 19	++	++	++	++	Exoph. Goitre Auricular Fibrillation
EW	6	154	28	♀	98.0	49.0	1284	+14	100	130	0	Tr	0	0	0	0	98/ 145	68/ 76	108/ 120	25/ 28	++	+	+	+	Toxic Adenomata
MvB	7	138	55	♀	98.6	42.5	1200	+43	110	60	0	C R	C R	Tr	0	0	++	168/ 190	68/ 88	104/ 124	24/ 28	+++	+++	+++	+++	Exoph. Goitre Toxic Adenomata
BB	8	161	51	♀	99.2	63.0	1445	+23	130	190	0	C R	C R	0	0	++	116/ 130	60/ 68	96/ 104	24/ 24	±	+	±	±	Toxic Adenomata
HG	9	168	30	♂	98.0	55.0	1551	+45	100	230	0	Tr	C R	0	0	++	164/ 130	110/ 68	106/ 120	30/ 24	++	++	++	++	Exoph. Goitre Hypertension On Ward
FP	10	170	32	♀	98.6	43.3	1214	+31	100	110	0	C R	C R	Tr	0	0	++	130/ 140	74/ 80	110/ 100	32/ 24	+	+	+	+	Exoph. Goitre
MS	11	171	28	♀	99.2	56.4	1395	+10	-	-	-	-	-	-	-	N.T.	142/ 115	82/ 72	94/ 92	26/ 28	0	±	±	0	Toxic Adenomata
JB	12	203	29	♀	99.0	51.8	1449	+22	110	180	0	0	Tr	0	0	+	110/ 115	66/ 74	78/ 78	30/ 28	±	±	±	±	Toxic Adenomata
BR	13	206	45	♀	98.0	64.0	1392	+19	100	150	0	0	C R	C R	0	++	120/ 180	80/ 100	110/ 120	28/ 32	+++	+++	+++	+++	Toxic Adenomata Thyroid Ant Polyp
AA	14	211	39	♀	98.6	62.5	1482	+33.6	120	90	0	Tr	0	0	0	±	126/ 150	62/ 64	110/ 120	35/ 26	++	++	++	++	Toxic Adenomata
RB	15	212	39	♀	98.6	56.4	1264	+11	110	140	0	C R	C R		0	++	130/ 134	68/ 76	104/ 116	28/ 32	0	±	±	±	Exoph. Goitre Toxic Adenomata
FB	16	215	25	♀	98.2	51.4	1433	+17	100	100	0	C R	C R	0	0	++	96/ 110	72/ 66	96/ 112	24/ 36	++	++	++	++	Exoph. Goitre Toxic Adenomata Pregnancy
GS	17	229	32	♀	99.0	59.2	1549	+34	100	200	0	0	C R	0	0	++	88/ 110	86/ 80	120/ 120	24/ 28	±	±	0	±	Exoph. Goitre Toxic Adenomata
GT	18	232	39	♀	98.4	54.5	1400	+11	110	130	0	0	0	0	0	0	110/ 124	64/ 68	76/ 108	28/ 36	+	+	+	V	Thyroid Adenomata Systolic
EB	19	235	55	♀	98.0	44.0	1403	+15	130	340	0	0	C R	CR	C R	+++	124/ 146	72/ 80	96/ 120	25/ 28	+++	++	++	+++	Exoph. Goitre Auricular Fibrillation
MF	20	245	53	♀	98.8	55.8	1524	+30	100	190	0	C R	C R	Tr	0	++	114/	90/	118/	/	-	-	-	N.D.	Exoph. Goitre Hypertension
PL	21	249	28	♀	99.0	51.2	1427	+14	90	100	0	Tr	Tr	0	0	+	130/ 150	68/ 80	88/ 96	30/ 30	++	+	+	+	Exoph. Goitre
MC	22	263	52	♀	98.6	48.8	1476	+36	130	120	0	0	0	0	0	0	98/ 110	60/ 64	110/ 114	30/ 28	++	++	++	++	Thyroid Hyperplasia Hypertension

TABLE I—Hyperthyroid cases

Key to column headings on tables: Basal metabolism test:

Weight: Figures given represent net weight in kilograms.

Calories: Figures given represent calories per square meter per hour.

Metabolism: Figures given represent percentage variation from normal for an individual of same age and sex.

The column headings under the glucose tolerance test represent time intervals following administration of glucose.

Figures under columns entitled pulse, blood-pressure (systolic and diastolic), and respiration represent values obtained before injection of adrenalin (figure to left of oblique line) and the maximum rise or fall following the injection (figure to right of line). By this graphic method the maximum rise of pulse, systolic blood-pressure and respiratory rate can be readily noted in each individual case as well as the maximum drop in diastolic pressure.

The degree of subjective and objective change following the adrenalin injection is noted by the number of plus signs in the columns entitled subjective and objective respectively, the scale running as follows: Plus-minus, doubtful; one plus—slightly noticeable; two plus—definite; three plus—marked.

N. D. = Not done.

V. = Vascular type of response; described elsewhere by O'Hare.

twelve were carried out by the same observer in order to eliminate as far as possible differences in interpretation. As was done in the case of the glucose tolerance test, an arbitrary scale was established in order to quantitate approximately the degree of response as follows:

Plus minus (±), cases showing a degree of response probably within the limits of normal:

1. Rise of pulse or blood-pressure, or both, of more than ten points, without evidence of much subjective or objective disturbance.

INITIALS	SERIES NUMBER	LAB. NUMBER	AGE	SEX	BASAL METABOLIC RATE: BUCCAL TEMPERATURE	WEIGHT	CALORIES	METABOLISM	GLUCOSE TOLERANCE TEST: BLOOD: FASTING	BLOOD: 2 HOURS	URINE: FASTING	URINE: 1 HOUR	URINE: 2 HOURS	URINE: 3 HOURS	URINE: 4 HOURS	INTERPRETATION	ADRENALIN SENSITIVITY TEST: BLOOD PRESSURE: SYSTOLIC	DIASTOLIC	PULSE	RESPIRATION	OBJECTIVE	SUBJECTIVE	INTERPRETATION	REMARKS
																							II HYPOTHYROID CASES
S.G.	1	138	38	♀	98.0	64.0	27.9	-20	90	200	O	O	O	O	O	O	120/80	70/60	96/84	-/-	-	-	N.D.	Myxedema
L.C.	2	139	44	♀	97.0	63.0	27.3	-24	90	80	O	O	O	O	O	O	110/70	70/60	90/76	-/-	-	-	N.D.	Myxedema
E.R.	3	144	46	♀	98.0	59.0	23.2	-23 ?	-	-	-	-	-	-	-	N.D.	130/-	70/-	110/-	0/-	O	O	O	Myxedema
B.T.	4	174	30	♀	97.8	59.5	30.7	-19	110	150	O	-	C.R.	Tr.	O	++	150/120	94/76	78/108	20/26	++	++	++	Migraine
T.C.	5	179	15	♀	97.0	43.7	27.5	-23	90	80	O	O	O	O	O	O	85/60	70/50	80/104	18/26	++	+	++	Thyroid Adenoma? Puberty
R.S.	6	183	48	♀	98.1	67.3	27.7	-36	90	90	O	O	O	O	O	O	130/100	70/70	70/72	18/22	±	±	±	Migraine Menopause
E.R.	7	213	46	♀	97.0	61	33.7	-33	100	100	O	O	O	O	O	O	110/100	70/70	90/104	16/16	++	++	++	Menopause
B.T.	8	217	11	♂	99.0	32.0	30.0	-28	100	60	O	O	O	O	O	O	?-	?-	90/-	20/-	-	-	N.D.	Cretinism
M.W.	9	227	24	♀	98.0	58.0	21.0	-43	100	110	O	Tr.	Tr.	O	O	+	98/110	66/90	84/84	18/24	+	+	+V	Hypothyroidism Arteriosclerosis
H.	10	234	29	♀	98.0	66.0	29.0	-20	110	110	O	O	O	O	O	O	96/130	70/96	82/116	16/32	++	++	++	Migraine
S.A.	11	246	42	♀	98.0	60.0	27.6	-23	100	190	O	O	O	O	O	±	-/-	-/-	78/-	-/-	-	-	N.D.	Menorrhagia
M.C.	12	118	43	♀	98.4	61.3	26.2	-28.3	90	110	O	O	O	O	O	O	120/80	80/70	80/96	20/16	++	+	++	Rt. sciatica? fatigue
H.K.	13	192	48	♀	98.0	96.2	24.9	-39	140	250	O	C.R.	C.R.	C.R.	O	+++	170/120	110/90	70/96	24/28	±	O	O	Migraine Menopause

TABLE II.—Hypothyroid Cases

2. Slight subjective and objective disturbance without perceptible rise of pulse and blood-pressure.

One plus (+), slightly positive response. Rise in pulse and blood-pressure of over ten points, with slight but definite subjective and objective disturbance.

INITIALS	SERIES NUMBER	LAB. NUMBER	AGE	SEX	BASAL METABOLIC RATE: BUCCAL TEMPERATURE	WEIGHT	CALORIES	METABOLISM	GLUCOSE TOLERANCE TEST: BLOOD: FASTING	BLOOD: 2 HOURS	URINE: FASTING	URINE: 1 HOUR	URINE: 2 HOURS	URINE: 3 HOURS	URINE: 4 HOURS	INTERPRETATION	ADRENALIN SENSITIVITY TEST: BLOOD PRESSURE: SYSTOLIC	DIASTOLIC	PULSE	RESPIRATION	OBJECTIVE	SUBJECTIVE	INTERPRETATION	REMARKS
																							III FATIGUE CASES	
L.M.	-	-?	30	♀	98.0	59.2	29.5	+1	110	120	O	O	O	O	O	+	120/90	80/64	86/84	18/24	+	+	+	Thyroid Adenoma? Hyperplasia
F.H.	2	118	27	♀	98.6	61.0	28.5	++	100	-	O	Tr.	Tr.	Tr.	O	+	120/90	80/70	84/84	18/18	+	+	+	Thyroid Hyperplasia Menorrhagia
R.R.	3	131	34	♀	97.0	59.3	31.2	0	130	110	O	Tr.	Tr.	O	O	+	130/90	70/70	84/84	18/24	++	++	++	High Thyroid Hyperplasia
M.D.	+	152	33	♀	98.8	58.8	31.3	-16	90	130	O	O	Tr.	O	O	+	120/80	70/60	84/84	18/24	++	+	++	Thyroid Hyperplasia
C.T.	5	156	26	♂	98.0	67.0	48.8	+9	100	100	O	O	Tr.	O	O	+	130/100	80/60	84/84	18/24	++	++	++	Thyroid Hyperplasia
R.B.	6	189	30	♀	97.0	64.8	37.7	+3	100	100	O	O	O	O	O	O	110/90	70/60	84/84	18/24	++	++	++	Thyroid Hyperplasia Menorrhagia Tachycardia
A.R.	7	190	28	♀	98.6	64.7	26.4	-26	100	160	O	Tr.	C.R.	O	O	++	130/80	80/60	84/84	18/24	++	++	++	Goiter, Mitral Thyroid, not enlarged
R.J.	8	196	30	♀	99.0	57.0	30.1	-13	80	70	O	O	O	O	O	O	120/80	80/60	84/84	18/24	++	++	++	Thyroid Hyperplasia Menorrhagia
L.C.	9	204	34	♀	97.4	61.0	35.3	-13	-	-	-	-	-	-	-	N.D.	120/80	80/60	84/84	18/24	+	+	+	Thyroid Adenoma?
B.R.	10	225	35	♀	98.0	50.0	34.4	0	130	130	O	O	O	O	O	O	110/80	70/60	84/84	18/24	+	++	++	Rt. adrenal Carcinoma
E.B.	11	196	19	♂	98.6	69.8	37.4	-9	110	90	O	O	O	O	O	O	120/80	80/60	84/84	18/24	++	++	++	Rt. adrenal Carcinoma Nephritis
P.K.	12	197	21	♂	98.4	59.3	35.5	-10	100	90	O	O	O	O	O	O	120/80	80/60	84/84	18/24	+	+	+	Eliot? Tyrotoxicosis
F.R.	13	204	24	♂	99.4	73.7	40.7	+26	130	100	O	Tr.	C.R.	Tr.	O	++	120/80	80/60	84/84	18/24	+	+	+	Acquired Athlete
M.R.	14	241	34	♀	98.8	55.0	28.6	-31	100	90	O	O	O	O	O	O	120/80	80/60	84/84	18/24	++	++	++	Tachycardia
E.V.	15	188	34	♀	99.2	48.2	33.5	-4	90	260	O	O	C.R.	Tr.	O	+++	120/80	80/60	84/84	18/24	++	++	++	Thyroid Hyperplasia

TABLE III.—Fatigue Cases.

Two plus (++), definitely positive response. Rise in pulse and blood-pressure of over twenty points, with increased degree of sub-

jective and objective disturbance to the point of considerable discomfort for the patient.

Three plus (+++), strongly positive response. Rise in pulse and blood-pressure of over thirty-five points with an alarming degree of subjective and objective disturbance.

INITIALS	SERIES NUMBER	LAB. NUMBER	AGE	SEX	BASAL METABOLIC RATE				GLUCOSE TOLERANCE TEST								ADRENALIN SENSITIVITY TEST						REMARKS
					BUCCAL TEMPERATURE	WEIGHT	CALORIES	METABOLISM	BLOOD		URINE						BLOOD PRESSURE		PULSE	RESPIRATION	OBJECTIVE	SUBJECTIVE	INTERPRETATION	
									FASTING	2 HOURS	FASTING	1 HOUR	2 HOURS	3 HOURS	4 HOURS	INTERPRETATION	SYSTOLIC	DIASTOLIC						
IN	1	39	27	♀	98.0	66.8	36.2	−1	130	190	O	Tr.	Tr.	O	O	+	135	90	76	—	++	++	++	IV MISCELLANEOUS CASES
HP	2	81	41	♀	98.0	87.9	36.5	+1	100	180	O	O	C.R	C.R	Tr.	++	124 / 104	78 / 66	80 / 76	20 / 20	++	++	++	
IO	3	136	36	♀	97.0	67.0	43.0	+14	150	150	O	O	O	O	O	O	132 / 114	72 / 52	108 / 96	22 / 22	+	O	±	
AG	4	131	42	♀	98.2	87.5	35.5	−2	100	110	O	O	O	O	O	O	94 / 102	64 / 58	100 / 84	18 / 24	+	+	++	
ND	5	134	40	♀	97.4	60.3	35.7	−1	90	100	O	O	O	O	O	O	104 / 120	66 / 72	104 / 108	18 / 28	++	++	++	
SB	6	140	45	♀	99.4	64.9	41.2	+12	90	130	O	C.R.	Tr.	O	O	+	91 / 118	66 / 82	76 / 82	18 / 28	±	O	±	
EJ	7	153	43	♀	98.4	72.0	37.4	−03	-	-	-	-	-	-	-	BD	144 / 176	88 / 90	92 / 100	— / —	+	+	+	
ES	8	136	36	♀	99.6	68.0	40.9	+13	90	110	O	O	O	O	O	O	110 / 126	72 / 84	80 / 88	20 / 28	++	+	+	
WV	9	150	36	♂	98.0	79.3	40.3	+2	110	100	O	O	O	O	O	O	118 / 128	74 / 80	100 / 92	16 / 28	O	O	O	
HH	10	163	32	♀	98.0	63.0	35.0	−4	90	100	O	Tr.	Tr.	Tr.	O	+	116 / 140	70 / 110	104 / 120	20 / 36	++	++	++	
AH	11	167	49	♀	98.6	70.0	38.3	+1	110	130	O	O	O	O	O	O	130 / 136	78 / 96	84 / 84	22 / 24	±	±	±	
ME	12	172	51	♀	98.4	58.0	39.3	+11	100	150	O	O	O	O	O	O	- / -	- / -	92 / 92	20 / 20	O	O	O	
EW	13	177	31	♂	98.0	68.2	38.4	+1	90	90	O	O	O	O	O	O	— / —	— / —	64 / 64	20 / 20	—	—	NB	
MS	14	178	22	♀	97.8	66.8	38.3	−36	100	140	O	O	O	O	O	O	96 / 128	72 / 76	72 / 108	24 / 32	++	++	++	
CK	15	180	28	♀	99.0	59.5	41.3	+15	100	160	O	Tr.	C.R.	Tr.	O	++	112 / 132	64 / 76	84 / 94	18 / 20	+	±	±	
AD	16	183	52	♀	97.0	64.6	32.8	−6	100	125	O	O	O	O	O	O	88 / 140	64 / 72	58 / 102	20 / 16	+	±	+V	
FH	17	185	23	♀	98.0	64.5	38.4	+6	90	115	O	O	O	O	O	O	110 / 126	64 / 68	84 / 108	18 / 20	++	+	+	
QD	18	199	28	♀	98.4	77.0	36.0	−2 7	125	125	O	O	O	O	O	O	96 / 112	74 / 84	78 / 84	22 / 20	++	+	++	
BA	19	201	30	♀	97.0	65.6	31.0	−15.5	100	160	O	O	O	O	O	±	122 / 132	76 / 78	84 / 92	18 / 20	++	++	±	
AW	20	208	29	♀	98.0	65.7	37.3	+1	110	110	O	C.R	O	O	O	+	104 / 116	62 / 72	72 / 92	18 / 20	++	++	++	
VE	21	205	33	♀	98.6	69.4	36.3	−14	90	250	O	C.R	C.R	C.R	O	+++	122 / 182	80 / 120	80 / 108	16 / 16	++	+	++	
LH	22	207	32	♂	98.2	82.6	39.4	0	90	230	O	C.R	C.R	C.R	O	+++	94 / 136	70 / 80	64 / 104	16 / 20	+	++	++	
BR	23	208	27	♀	98.6	63.0	39.7	−5	110	110	O	C.R	—	—	Tr.	++	128 / 146	64 / 76	96 / 120	24 / 32	++	+	+	
AS	24	210	19	♀	98.2	59.8	33.2	−13	110	90	O	O	O	O	O	O	96 / 138	62 / 76	88 / 96	24 / 20	+	+	+	
KW	25	216	35	♀	99.0	61.0	36.2	−1	130	125	O	O	O	O	O	O	136 / 168	80 / 84	88 / 104	18 / 20	++	+	+V	
MM	26	218	49	♀	97.8	57.0	35.0	+10	100	90	O	O	O	O	O	O	100 / 106	68 / 78	72 / 80	16 / 16	O	O	±V	
MV	27	230	31	♀	98.2	57.0	36.7	0	110	80	O	O	O	O	O	O	120 / 136	66 / 72	76 / 100	24 / 24	++	++	++	
PZ	28	236	30	♀	98.8	80.0	31.5	+4.4	150	150	O	Tr.	O	O	O	±	104 / 117	72 / 78	84 / 104	16 / 16	+	+	+	
MC	29	237	22	♀	98.6	42.0	37.6	+2	110	145	O	O	O	O	O	O	98 / 102	66 / 76	84 / 108	18 / 16	±	+	+	
NB	30	238	49	♀	97.8	58.0	30.5	−14	100	80	O	O	O	O	O	O	90 / 110	56 / 62	66 / 80	18 / 18	+	+	+	
EB	31	242	24	♂	97.6	70.5	35.7	−14.7	110	80	O	O	O	O	O	O	106 / 120	64 / 74	64 / 80	18 / 20	+	+	+	
DB	32	240	21	♀	98.4	76.3	29.5	−20	110	140	O	O	O	O	O	O	94 / 116	58 / 86	76 / 88	22 / 24	+	+	+	
FB	33	258	23	♀	98.0	65.0	31.6	−14.6	100	140	O	O	O	O	O	O	96 / 132	60 / 78	80 / 88	18 / 24	+	+	+	
CC	34	244	30	♀	98.0	79.5	30.0	−20	110	110	O	O	O	O	O	O	98 / 116	62 / 78	80 / 88	18 / 24	+	+	+	
LN	35	245	36	♀	97.0	63.4	33.6	−9	130	110	O	O	Tr.	O	O	±	96 / 94	80 / 84	84 / 84	24 / 28	±	±	O	

TABLE IV.—Miscellaneous cases.

Clinical Groupings. HYPERTHYROIDISM. All cases in this group may be classified under two headings: (*a*) True exophthalmic goiter and (*b*) toxic adenomata without exophthalmos. They all without exception presented a majority of the signs and symptoms ordinarily considered cardinal in the diagnosis of thyrotoxicosis (exophthalmos, restlessness, tachycardia, tremor, loss of weight and hyperhidrosis).

HYPOTHYROIDISM. Among the cases listed as hypothyroidism are included three in which an unqualified diagnosis of myxedema could be made clinically. The remainder, while presenting certain

findings suggestive of thyroid insufficiency, were not diagnosed until functional tests were carried out and the administration of thyroid extract had effected a disappearance or amelioration of the predominating symptoms.

FATIGUE CASES. We have considered it excusable to describe certain cases under this heading because of the predominance of subjective and objective fatigue in the clinical picture, and in spite of the fact that they cannot be classified among the recognized clinical entities. In this conception we do not claim priority, as Rogers[30] has already recognized the syndrome. We believe that most of these cases are identical with those described by Goetsch as cases of latent hyperthyroidism of a type hitherto unrecognized. They usually present in addition to subjective and objective fatigue, perceptible thyroid enlargement, labile pulse and vague symptoms ordinarily described as neurasthenia. Two of the cases showed palpable nodules in the thyroid while in three no enlargement could be demonstrated. One classical case of effort syndrome is included in this series.

MISCELLANEOUS. In this large and motley group we have placed cases which were studied with a view to the elimination of possible disturbance in the endocrine system. In some of them the existence of thyroid disturbance had been established at some previous period; in others clinical evidences of pluriglandular disturbance were present, though the variations in clinical findings preclude the possibility of placing them in definite categories; in a few all evidence of endocrine disease was found lacking and the presence of organic disease established, while another small group may be classed as essentially normal.

Discussion. In looking over the records of the cases here presented it appears quite evident that ordinary careful clinical methods are entirely satisfactory from a diagnostic standpoint in all cases of frank hyperthyroidism. However, in four of these cases (171, 215, 232 and 235) functional tests proved of distinct value in confirming a strong clinical impression of mild thyrotoxicosis. In the general run of cases these tests showed their greatest value in allowing a quantitative estimate of the degree of intoxication and in forming a basis for studying the effect of treatment.

A glance at Table I should convince any impartial critic that the only functional test showing an invariably positive response in cases of hyperthyroidism is the basal metabolism. However, it is evident that any subject of thyrotoxicosis must pass through an incipient stage in which functional tests might be expected to yield negative results. Our attention was directed to this possibility by the behavior of one case in particular (215) whose basal metabolic rate was plus 6 per cent at a time when several clinicians were convinced that her symptoms were due to hyperthyroidism. One month later subjective and objective signs had increased and her basal metabolic rate was found to have risen to plus 17 per cent.

Alimentary hyperglycemia and glycosuria have been found to be consistently present in hyperthyroidism, but inasmuch as these are also found to occur in other conditions, where their presence is sometimes difficult to explain, their value as specific tests of thyroid function is correspondingly diminished. Several workers have called attention to a characteristic blood-sugar curve occurring in hyperthyroidism, *i. e.*, a rapid rise in the blood sugar to a moderately high level followed by a rapid fall to the fasting level, as contrasted with the slow rise and fall which is common to diabetes. It has been suggested that this type of reaction is due to a rapid mobilization of sugar and that it is another manifestation of accelerated metabolism. Although we have not considered it necessary to make hourly blood-sugar determinations, we have noticed the tendency for glycosuria to occur usually within the two hours following the administration of glucose and for many cases to have a normal or nearly normal blood sugar at the end of two hours. The cases which showed this reaction most strikingly did not necessarily show an excessively heightened metabolism. In fact, there was no close agreement between the basal metabolic rate and the degree of intolerance to glucose. Thus, whereas five cases showed negative sugar reactions and a maximum basal metabolic rate of plus 36 per cent, six other cases whose metabolism was less than plus 36 per cent showed positive sugar reactions. In one case (255) the response was very marked, although the basal metabolism was only plus 15 per cent. It is to be noted, however, that this curve was similar to that described in potential diabetes, although no other evidence of the condition was found in this case.

In the adrenalin sensitivity test there was no direct relationship established between the intensity of the reaction and the basal metabolic rate. In fact, some of the strongest adrenalin reactions were observed in which the metabolism was less than plus 25 per cent, and *vice versa*. Two cases having a basal metabolic increase of over 50 per cent showed a reaction to adrenalin which, according to the standards proposed by Goetsch, would be construed as negative.

As far as a comparison can be drawn between the glucose tolerance test and the adrenalin sensitivity, it may be said that in looking over the hyperthyroid series some degree of similarity may be traced in the results observed. This correspondence, however, is not constant and is not sufficiently marked to allow an accurate forecast of the result of one of those tests in a given individual on the basis of the response observed to the other.

It will be noticed that several of the positive adrenalin reactions are designated as vascular in type. By this is meant that the rise observed in pulse and blood-pressure was not as sustained as in the cases showing the type of response alleged to be typical of hyperthyroidism. In the hyperthyroid group three of the four showing

a vascular response had no hypertension, although showing evidence of bloodvessel disease, whereas three cases of hypertension showed the typical sustained rise of pulse and blood-pressure, this rise being equally high with that noted in the vascular type (rise in the systolic pressure of at least fifty points).

One noteworthy observation that is suggested by a study of the records in the hypothyroid group is that the glucose tolerance test was found to be distinctly positive in only two cases, both of which showed severe headache of the migraine type as the only symptom. In one of these the evidence was very suggestive of associated pituitary disease. On the other hand, of those which were subjected to the adrenalin test, 55 per cent showed a definitely positive response. These cases were all distinctly improved by the administration of thyroid extract. We regard this fact as the strongest clinical evidence hitherto adduced that the adrenalin test in itself affords no criterion of the presence or absence of thyrotoxicosis. No correspondence could be established between the basal metabolic rate in these cases and the response to glucose and adrenalin.

Among the fatigue cases it will be noted that in 40 per cent the basal metabolic rate was minus 10 per cent or less while in the remainder it fell within normal limits. In no case was an increased metabolism demonstrated. We feel that at the present time it is impossible to say whether or not these cases which show a lowered metabolism are definitely hypothyroid, as we have not had the opportunity to carry the therapeutic test to a satisfactory conclusion. In one case (190) in which the basal metabolic rate was minus 26 per cent and the response to adrenalin distinctly positive, thyroid extract was tolerated well and was administered long enough to bring the metabolism to normal—a change which was unaccompanied by improvement in her clinical condition. Goetsch[21] and Woodbury[20] have recently advanced the view that cases of this type show clinical improvement following thyroidectomy, and state that the excised glands show a picture of diffuse adenomatosis with an increase in the mitochondrial content of the cells and other signs of increased functional activity. We are therefore watching our cases with eagerness for the development of clinical evidences of hyperthyroidism—the more so because with one exception all of them responded positively to adrenalin.

In view of the magnificent quantitative work of Kendall[31] and Plummer,[32] which has shown the definite relationship between thyroxin and the basal metabolic rate, it does not seem rational to make a diagnosis of hyperthyroidism, in the absence of the classical symptoms and signs of this condition, when the basal metabolism is within normal limits. The possibility of the existence of a second active principle in the thyroid gland, independent of thyroxin and with a different physiological action, has been suggested. Up to

the present time there is not sufficient clinical or physiological evidence to afford this theory much support. Although both Goetsch and Woodbury claim clinical improvement in almost all their cases following thyroidectomy, in no instance had their patients been followed over a period exceeding nine months. Furthermore, we do not feel that the degree of subjective improvement reported is sufficiently striking, in the absence of careful control by direct personal observation and the repeated use of functional tests, to justify any dogmatic statement on this most important point. Particularly is this true since the psychological effect of operation and the recognized value of a subsequent rest period might together be sufficient to produce a definite, if temporary, amelioration of symptoms. We must not be unmindful of the danger of hypothyroidism developing in these cases as a result of thyroidectomy. As far as we know no report has yet been published of basal metabolic estimations following these operations.

In regard to the glucose tolerance test 20 per cent of the fatigue cases showed a moderately and another 20 per cent a slightly diminished tolerance, while the rest showed doubtful or negative reactions. No relationship could be demonstrated between this response and the basal metabolism or adrenalin sensitivity tests.

In the large and varied miscellaneous group a few points of interest are to be noted: One case only (173) showed a decided increase of the basal metabolic rate. This patient had a definite pan-sinusitis and showed no clinical evidences of hyperthyroidism or of disease of any other endocrine organ. Five cases showed increases of from 10 to 13 per cent; 2 of these were cases of Raynaud's disease, 1 of active pulmonary tuberculosis, 1 of vertigo of vestibular origin and 1 of arteriosclerosis with menopause. Three of these were individuals of unusually short stature, while with one exception they all showed an exceptionally poor state of nutrition. These facts may in part account for an apparent slight increase in their basal metabolic rate. On the other hand 11 cases showed a decrease in the metabolic rate of from 12 to 24 per cent. Of these 8 were considered to be possible hypothyroid cases and were given thyroid gland. They were left, however, in the miscellaneous group because the period of observation was not considered long enough to warrant a final diagnosis of hypothyroidism. Of this small group of 11 cases showing decreased metabolism 4 were distinctly sensitive to adrenalin and 5 slightly so, the remaining 2 giving a questionable response.

Five cases in the whole miscellaneous group showed distinct intolerance to glucose, 2 of which were clinically well following definite hyperthyroidism. One case had Raynaud's disease, 1 paroxysmal tachycardia and 1 mucous colitis.

In regard to the adrenalin sensitivity test, excluding those cases showing a decreased metabolism, 40 per cent showed a dis-

tinctly positive response and 20 per cent a mild one. Thus on calculating the number of definitely positive responses to adrenalin in the whole series of 85 cases we find that there were 40, (47 per cent). Of these 10 were seen in the hyperthyroid group (45 per cent), 5 in the hypothyroid group (38 per cent), 10 in the fatigue group (66 per cent) and 15 in the miscellaneous group (45 per cent). On the basis of these figures we consider that the phenomenon of hypersensitivity to adrenalin may occur in a variety of disease conditions which have not as yet been exhaustively studied from this angle.

Summary and Conclusions. A clinical and functional study is presented of 85 cases showing symptoms either definitely attributable to disturbance of the endocrine glands, particularly the thyroid, or not readily explainable on any other basis.

The functional tests employed were the basal metabolism, glucose tolerance and adrenalin sensitivity tests.

The cases studied were divided into four groups: hyperthyroid, hypothyroid, fatigue and a large miscellaneous group.

Clinical methods were found satisfactory in the diagnosis of frank hyperthyroidism, myxedema and to a lesser extent in the third and fourth groups. In apparent hypothyroidism—not myxedematous in type, however—the ordinary clinical methods usually failed to suggest the probable diagnosis. In such cases the diagnosis was made entirely on the basis of a decreased basal metabolic rate, together with definite improvement after the administration of thyroid extract.

Of the functional tests used the basal metabolism was the only one to yield uniform results, which could be reasonably interpreted in association with the clinical findings and subsequent progress of the cases studied. As a result of this study it is our firm conviction that an apparatus for the determination of the basal metabolic rate is indispensable in a diagnostic clinic. We share the belief of other workers that this test affords the best index of the degree of thyroid activity.

Both of the other tests yielded positive results in almost all cases of hyperthyroidism, but the frequency of similar responses in a variety of other conditions, in some of which the diagnosis of hyperthyroidism was not even a remote possibility, necessarily detracts from their value as specific tests of thyroid function.

Special emphasis is laid on three points brought out by the data here presented. These are: (1) That there are some cases showing definite hypersensitiveness to adrenalin and intolerance to glucose who tolerate thyroid extract well and improve under its administration; (2) that it is dangerous to attribute much importance to a positive adrenalin response in the diagnosis of suspected hyperthyroidism; and (3) a corollary of the point just mentioned that an occasional case of classical exophthalmic goiter showing marked

increase of the basal metabolic rate may exhibit no hypersensitiveness to adrenalin.

We wish to take this opportunity of expressing our appreciation to the physicians and surgeons of the Buffalo General Hospital for the privilege of studying their cases, their interest in the work and for many valuable suggestions, as well as to the hospital administration, through whose good will it was possible to use the personnel and equipment of the routine laboratory, although no special financial provision had been made.

We also wish to thank Miss Helen Markey and Miss Mary B. Watters, laboratory assistants, for their tireless energy in making the many chemical determinations, and Miss Blythe Gager, for assistance in the performance of the adrenalin sensitivity tests.

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A CLINICAL CLASSIFICATION ON ASTHMA BASED UPON A REVIEW OF SIX HUNDRED AND FORTY-EIGHT CASES.[1]

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It is clearly recognized today that asthma is always a symptom and never a disease as such. The diagnosis is usually made by the patient. The term "asthma" is here used to include all those cases in which a type of dyspnea characterized by difficult inspiration or expiration, or both; "wheezy" breathing is the predominant symptom. Such breathing occurs in a variety of conditions. The patient with a typical barrel chest full of squeaks and musical rales over which the breath sounds are prolonged usually has asthma, but his diagnosis should be pulmonary emphysema. Bronchial asthma is a loose term which is ordinarily applied to those patients with asthma in whom the physical examination between the attacks is essentially normal. As to the mechanism by which this peculiar type of dyspnea is produced we know little, although the theory of bronchial spasm with edema of the mucous membrane seems adequate.

[1] From Anaphylaxis Clinic of the Massachusetts General Hospital, Boston, Mass.

In the study of each case of asthma at least two factors in its cause are important. There is for each case of asthma an underlying basis the nature of which is quite unknown, except that it tends to be inherited, especially in those cases in which the asthma is due to foreign proteins. This basis may be referred to as the "asthmatic state" which underlies not only the various forms of asthma but such other conditions as hay fever, food and drug idiosyncrasies and certain cases of urticaria, angioneurotic edema, eczema, etc. On top of this basis recent investigation has identified a variety of types of asthma which it is the purpose of the present paper to review, with particular reference to their relations one with another.

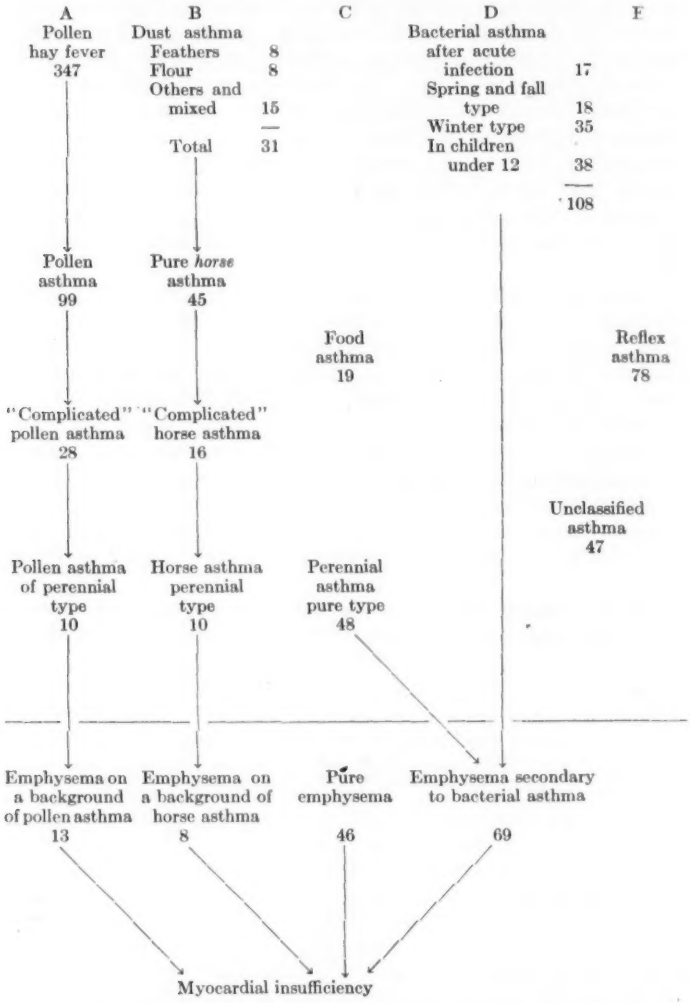
The simplest and most obvious classification already discussed, especially by Walker and by myself, divides asthmatics into two main groups: First, those sensitive to foreign proteins in which the cause is outside of the body (extrinsic), and second those not sensitive where the cause is inside of the body (intrinsic).

During the past three years patients with asthma have been studied in the clinic for anaphylaxis at the Massachusetts General Hospital and in private practice. The accompanying chart shows an arrangement of these cases and is an attempt to demonstrate the clinical relation in the various groups. In the management and treatment of cases this chart has been found to be of great practical value.

Foreign proteins may enter and act upon the body in several ways, particularly through the respiratory tract, as in Groups A and B of the chart and through the gastro-intestinal tract, as in Group C.

Group A. Pollen Hay Fever and Asthma. Group A represents cases which were sensitive to the plant pollens. There were 71 cases of early hay fever (sensitive to the graminaceæ, timothy, red top and June grass), 227 cases of late hay fever (sensitive to the compositæ ragweed) and 49 cases of double hay fever—a total of 347 cases of hay fever. (These cases of simple hay fever are not included among the 648 cases of asthma.) Pollen asthma describes the asthma which occurs as an aggravation of hay fever. Pollen asthma must, in its pure form, be limited in its dates of onset and subsidence to the true hay fever season. Pollen asthma occurred in only 9 cases of early hay fever (12.6 per cent), in 81 cases of late hay fever (35.7 per cent) and in 9 cases of double hay fever (18.3 per cent), "and in a total of 99 cases (28.5 per cent) of all types of hay fever." This is the most typical form of asthma known: the easiest to diagnose and the simplest to treat. Desensitization with pollen extract relieves this asthma even better than it relieves hay fever.

A CLINICAL CLASSIFICATION OF 648 CASES OF ASTHMA.



In certain cases this pollen asthma once started does not end abruptly with the end of the hay fever season but continues on into the fall or winter. Such cases, 28 in number and nearly 28 per cent of the 99 cases of pollen asthma, are here called cases of complicated pollen asthma. This term is, however, applicable only to those cases in which asthma continues in one single attack, which lasts not more than a few weeks beyond the true hay fever season.

Some cases which give a history compatible in the early stages with a pollen asthma—and later with a complicated pollen asthma—will say that still later, after the apparent end of their usual fall attack, they will have other attacks during the winter and spring. It is obvious that these other attacks of asthma can have no relation to any pollens and must therefore be due to bacterial action or in certain cases to some reflex action. It might be presumed that other foreign proteins in dust or food might perhaps be responsible for the later attacks in such patients, and, indeed, 7 patients reacted positively to one or other cereal proteins and 1 of them to eggs as well. However, in the 7 cases the removal of the corresponding food had no effect on the asthma.

The diagnosis of pollen asthma can be made in most cases by a careful history and without skin tests. Occasionally a case of supposed pollen asthma was found that failed to react to pollens. Study, however, revealed the fact that such patients had no eye or nose symptoms preceding their asthma, which of course emphasizes the importance of care in history-taking.

Up to this point the physical examination of these patients between their attacks of asthma is always normal. As the asthma progresses, as the attacks become longer and the intervals shorter, evidence of a secondary pulmonary emphysema develops. This will be discussed at greater length later. Suffice it to say that of the 99 cases of pure pollen asthma, 23 cases went on to develop perennial asthma, and 13 of these had emphysema. Two cases which had late hay fever and also had a perennial asthma had never been worse during the fall, so that in them a diagnosis of pollen asthma was not made.

Group B. Dust Asthma. Group B is a group closely related to Group A, and includes 76 cases of individuals sensitive to foreign proteins other than the pollens, but is confined to those cases in which the contact is by way of the respiratory tract, and in which the exposure is to proteins in dust. Here are 45 cases of horse asthma, 9 of which were sensitive to the pollens as well and one of which reacted to egg-white. In addition there are 8 cases of asthma due to feathers, 8 cases of asthma in bakers and housewives due to wheat flour dust, 1 case due to cats and 1 to dogs, 1 to coffee, and 11 cases of asthma due to some unknown dust, only 6 of which had positive tests, and these tests were incompatible with the history. In this last group of 11 cases this diagnosis was made because of the peculiar circumstances: a theater, a musty house or a farm which invariably precipitated the attack. It is felt that more comprehensive tests might have revealed the offending protein, for as long as the patient avoided the particular circumstances there was no asthma. Walker, quoting Goodale, has lately defined such cases as reflex in nature (through the olfactory nerves).

The 8 cases of asthma from wheat flour dust are of great interest. They were all in bakers. In spite of the fact that they gave satisfactory tests to the wheat proteins they had no symptoms at all referable to eating white bread. Symptoms developed only during or shortly after exposure to wheat flour in the form of dust. In other words, symptoms were caused only by contact through the respiratory tract. Treatment, however, included the withdrawal of cereals in the diet, as a cumulative action is a distinct possibility. Cases of susceptibility to other dusts, such as orris-root powder, rice powder, rabbit, guinea-pig and miscellaneous hair, perhaps leather dust and a variety of others, should be mentioned for the sake of completeness, although in the present study no such case was identified. In an analysis of 198 cases of vasomotor rhinitis susceptibility to orris-root powder was found in 13 (6 per cent), but none of the patients had asthma.

As in the case of pollen asthma, so horse or dust asthma may readily be complicated by bacterial infections to a greater or less extent, and these complications may ultimately produce emphysema. In this Group B, 16 cases in the total of 76 were so complicated and 10 went on to develop perennial asthma, and 8 of them emphysema as well.

Group C. Food Idiosyncrasy. Group C represents those individuals who are obviously poisoned by certain definite foods or food combinations. This poisoning manifests itself by asthma, by urticaria, by angioneurotic edema or occasionally by violent gastro-intestinal upsets or by eczema.

In 19 cases, or only 3 per cent of the 648 cases of asthma, proteins in food were considered to be the cause, not only because each patient gave a well-marked test to the protein in question, but also because the patient's symptoms were definitely relieved when the particular food was eliminated.

These 19 cases were sensitive in 10 cases to egg, in 4 to wheat, in 2 to meat and in 1 each to nuts, fish and milk; 4 cases were sensitive each to a number of different foods, the most frequent combination being to eggs and wheat. Eleven of these 19 cases were in children. It so happened that no case of food asthma in this series was found which had a complicating bacterial asthma.

Thirty-five cases of urticaria and 6 cases of angioneurotic edema have been tested[2] but no case of either urticaria or angioneurotic edema was found to have asthma.

Twenty-nine cases of eczema were tested and 5 of these also had asthma which seemed to come and go with the eczema. Four of these 5 cases had positive tests each to one or more food proteins.

Group D. Bacterial Asthma. Group D represents perhaps the most common group, which can be subdivided as follows:

[2] For results see paper on Skin Tests with Foreign Proteins, which will appear in an early issue of this Journal.

1. Where asthma dates from a definite acute respiratory infection, 17 cases (13 adults and 4 children).

2. Eighteen cases in which there is each year a rather sharp and severe but relatively short attack of asthma occurring with the first cold spell of autumn and often recurring with the violent changes in temperature in March. Seven of these 18 cases were in male adults over thirty-five years old.

3. Thirty-five cases of "winter" asthma where the symptoms are closely associated with the cold weather of New England; are persistent and present practically constantly until the spring. Any fresh cold makes them markedly worse. All of these cases were in adults. Their separate classification is perhaps artificial, since many cases closely resemble the cases of perennial asthma to be discussed later. The group should be recognized, however, because a change to a warmer climate is an efficient and valuable treatment.

4. Bacterial asthmas in children, 38 cases, which come on most often after a cold and last for variable periods—the important point being that between the attacks these children are quite well. In case they are not quite normal between the attacks and still retain a certain amount of wheezing and dyspnea on exertion, it is usually found that they have mild emphysema, large peribronchial lymph nodes or some other organic cause for the symptoms. In each of these subgroups the tests are ordinarily negative, but 7 children have been added in spite of a positive test, since nothing in their story seemed to agree with the test.

Group E. REFLEX ASTHMA. While it is usually accepted that in many cases asthma depends upon the action of foreign proteins, yet in other cases the relation of proteins to the etiology is much less clear. In many of these latter some organic condition outside of the respiratory tract can be discovered and can be assumed to be indirectly responsible for the asthma, although the precise mechanism of its effect is usually unknown.

In the present study 78 cases are placed under the heading of reflex asthma. In 16 of these cases, mostly in children, bad nutrition was considered to be the cause rather than the result of the asthma, largely because treatment directed toward the regulation and enlargement of the diet, but without attention to specific foods, caused a great relief of the asthma. In at least 4 cases the asthma was associated with and presumably due to a faulty posture with ptosis. In 4 cases with disturbances of the gastro-intestinal tract, asthma was associated with constipation, the relief of which relieved the asthma. In 9 cases with diseased tonsils, 1 with lung abscess, 4 with bad teeth, and 11 with chronic pulmonary tuberculosis the absorption of toxic material is easy to understand, as at least a contributory cause to poor general condition and asthma. In 8 cases various pelvic disturbances were associated with the asthma, including the menopause and pregnancy, and in 2 cases asthma was invariably associated with the catamenia.

Referring to the definition of the term asthma as given in the first paragraph of this paper, it is of interest to note that recently a patient was referred to the writer for asthma in whom a tumor, probably luetic in nature but of sufficient size to obstruct the breathing, was found in the bronchial mucous membrane.

In the group of reflex asthma also are placed 13 cases of nervous asthma in which excitement or association with some disagreeable undertaking (return to college, beginning summer work, preparations for a journey) was the exciting cause of asthma in these patients with a general nervous instability; and finally, in 5 cases asthma seemed to follow a long period of stress and strain. Several of these latter cases have been undoubted results of the war, and a prolonged period of rest and relaxation, without other treatment, has caused a great improvement.

One case of this type is that of a widow who, left entirely alone, broke down under the strain of settling her husband's estate, sending the children to school and trying to do all the housework when her servants abandoned her. With a complete rest and change of environment the asthma largely disappeared.

Perennial Asthma. It is obvious that as asthma progresses the attacks become more frequent and of greater duration, but as a diagnosis of emphysema cannot be made in these cases, this waystation in the chart is justified. It would only be confusing to attempt to trace here the origin of the many cases of perennial asthma: but for the treatment of each case, this origin must be traced, if good results are to be obtained.

In addition to 23 cases in Group A and 10 cases in Group B who have reached this stage of perennial asthma there is a group of 48 cases who state in their history that their asthma has from its start been chronic with comparatively short intervals between attacks. Most, if not all, of these cases are of bacterial origin—their skin tests are all negative. Their separate classification is artificial and perhaps unnecessary.

Emphysema. On the chart a horizontal line is drawn between perennial asthma and emphysema. This line represents the onset of a demonstrable organic change in the patient which will remain constantly present even though the patient is sure that he "is entirely well."

Such patients have dyspnea on exertion which is usually associated with wheezing. If they are examined at any time, even between their attacks of asthma, they will show a more or less barrel-shaped chest with rounded shoulders. The breath sounds are most often diminished in intensity and high pitched in quality. Musical, whistling or squeaky rales are almost always present or can be brought out if the patient coughs a few times. In well-marked cases the pulse is often of poor quality: there is usually some cyanosis depending on the amount of associated bronchitis; the pulmonic

second sound is accentuated, due to the increased intrapulmonary pressure, while the heart seems on percussion to be small, due to the overlying lung. Such patients suffer from a markedly increased dead space in their air passages and from a markedly diminished vital capacity due to the large amount of retained air which they cannot expel.

Such patients are prone to develop chronic infections of the bronchi which are very resistant to treatment, in that these infections aggravate the emphysema just as the emphysema aggravates them, so that a vicious cycle is promptly established.

Emphysema may be acute compensatory following a severe attack of asthma. It may be idiopathic—that is, may be itself the primary condition arising in an unknown manner and not following an attack of asthma, and finally it may obviously be a late secondary result of chronic asthma.

In this series a total of 136 cases are diagnosed emphysema. Thirteen have already been included under pollen asthma, 8 under dust asthma and 4 under reflex asthma. Of the other 111 cases 14 gave a positive skin test to one or more foreign proteins, ragweed pollen, horse-hair extract and the wheat proteins being the most common. These cases have not been included in other groups because there was no history of hay fever or horse asthma which might have justified the test-finding. Twenty-one of these 111 cases were acute and of less than two years' duration. Twenty-five cases followed a history of chronic asthma and were of over twenty years' duration.

That prolonged emphysema with its associated chronic bronchitis may lead to myocardial insufficiency and arteriosclerosis seems undoubted whether the cause depends upon the burden to the circulation added by the almost constant effort to breathe or whether the cause is referable to the absorption of toxic material from the bronchi. It is, however, difficult to tell in just how many cases the myocardium is damaged, so that no figures can be given here.

In the foregoing, 648 cases of asthma have been discussed and classified. In addition to the above, 47 cases, or nearly 7 per cent of the whole, remain to date unclassified, most of whom have not been seen since their first visit.

Treatment. Treatment depends, obviously, on the type of asthma from which the patient suffers. Treatment by removal of foreign proteins or by attempts to desensitize the patient to them is sufficient in certain cases. On the other hand the treatment of perennial asthma, for example, will never be satisfactory until the etiology of each case is worked out. In the cases classified below, the "line of organic change," no treatment will be entirely satisfactory, although much can be done for the patient's comfort. In the cases above the line everything possible should be done to prevent the progress of the disease downward, and the hope of success is not unreasonable.

The chief function of such a classification of asthmatics, as is described above is, of course, to aid in the treatment of these patients. As is seen, most of the cases of asthma have neither a basis of definite foreign proteid susceptibility nor have they any abnormality which might justify a diagnosis of "reflex asthma," so that most of the cases come under the heading of "bacterial asthma" or, at all events, are complicated by bacterial infection. The subdivisions of this great group of bacterial asthmatics as given here are made on an empirical basis, usually not founded on any definite scientific basis but simply depend upon clinical observations and characteristics. In practice, however, these subdivisions have been found to be of some importance in treatment.

Vaccines have come to play an even more important role in the treatment of asthma, although their value from the strictly scientific viewpoint is as yet unknown. If it is assumed that the attacks of asthma depend upon a low-grade focus of bacterial action, say in the bronchial tubes, and if the use of vaccines is found to relieve these symptoms, it may be assumed that this relief depends upon the irradication, permanent or temporary, of this focus, and this irradication in turn is probably caused by the production of an active immunity. The possibility that the patient may be sensitized to bacteria and that the results of vaccine treatment are good because of a production of desensitization is another theory. There is little or no scientific basis available to date to help us choose between these two theories. The second theory has been advanced largely because of the desire to correlate all these cases with the simpler and more obvious cases of pollen and other foreign proteid sensitiveness. At all events it should be borne in mind that vaccines produce their greatest effect, at least in other conditions than asthma, by producing an active immunity, and therefore it may be assumed that vaccines will work best in those cases of asthma whose attacks are isolated by fairly definite intervals of more or less complete freedom from symptoms.

Another point about vaccines: in a previous paper the writer attempted to show that vaccines do good in asthma only in case a local reaction is produced at the site of inoculation. This finding has been many times confirmed and in many cases has furnished a method by which the proper vaccine for treatment has been selected. This method consists roughly in making separate vaccines from each of the various organisms isolated from the patient's sputum and then giving small doses of each vaccine subcutaneously. In twenty-four hours the local reactions from one or two of these vaccines may be fairly definite (heat, redness and tenderness), while there will be no reaction from the other strains used. If this is found to be the case, treatment with the organisms producing the reaction will usually give satisfactory results, whereas if the other non-reacting organisms are used in vaccines the further doses can be tremen-

dously increased without producing either local reaction, aggravation or improvement of the symptoms.

The object of this paper will have been attained if it has emphasized that not only are there many forms of asthma, but also by proper classification and by proper selection of the form of treatment a great deal can be done for these unfortunate sufferers.

Conclusions. 1. A chart showing the interrelation of various groups of asthmatics is presented in the hope that it will prove of service in the classification of these patients.

2. The importance of a careful study of the patient, and especially of his history, is emphasized.

3. The importance of a proper classification and of a knowledge of the origin of asthma in any given case as a precursor to the successful treatment of that case is demonstrated.

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OBSERVATIONS ON THE TREATMENT OF AURICULAR FIBRILLATION BY QUINIDIN SULPHATE.*

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Quinidin, one of the cinchona alkaloids, was isolated as a pure base by Van Heijningen in 1848. It is chemically isomeric with quinin and has somewhat similar physiologic properties. Occasionally it has been used in therapeutics as a substitute for quinin, particularly in the treatment of malaria.

Quinin was recommended as a remedy in heart disease seventy years ago by Beletti.[1] Such distinguished authorities as Huchard and Lancereaux considered it of value in cardiac palpitation, tachycardia and vascular erethism. According to Wenckebach, quinin was often used by the older clinicians in combination with digitalis. Nevertheless, its use in cardiac therapy was practically abandoned until Wenckebach,[2] by accident, discovered its effect in restoring normal rhythm in a case of auricular fibrillation. He then tried it a number of times, but was successful in restoring the normal rhythm in but one additional case.

Wenckebach's observations stimulated a number of studies of the effect of quinin on abnormal rhythms. It has been definitely established that quinin exerts an inhibitory effect against auricular fibrillation, but the percentage of cases in which the normal rhythm can be restored is so low that the use of the drug in clinical medicine for this purpose is scarcely warranted. Frey[3] studied the effects of the three other well-known cinchona alkaloids, namely, cinchonin, cinchonidin and quinidin. The first two he found to be of no particular value in interrupting fibrillation, but quinidin yielded striking results in auricular fibrillation and flutter. Of the first 22 cases treated, 11 regained the normal type of rhythm.

Comparatively little experimental work in respect of the effect of quinidin on the heart has thus far been reported, so that the information on this point is somewhat fragmentary. Santesson,[4] in 1893, studied its effects along with those of quinin, cinchonin and cinchonidin on the frog's heart. He concluded that its toxicity is about one-half that of quinin, as it required nearly double the con-

* Read in part before the Section on Medicine, College of Physicians of Philadelphia, October 24, 1921.

[1] Quoted from Pezzi and Le Clerc: La Médecin, March, 1921, p. 443.

[2] Die unregelmässige Herztätigkeit und ihre klinische Bedeutung, Leipzig and Berlin, 1914.

[3] Berl. klin Wchnschr., 1918, **55**, 417 and 450.

[4] Arch. f. exp. Path. u. Pharm., 1893, **32**, 321.

centration to bring about complete cardiac arrest. Both cause reduction of pulse volume and frequency, but while quinin tends to influence volume more than frequency, quinidin exerts comparatively more effect on frequency. Occasionally quinidin brought about actual increase in pulse volume. All the cinchona alkaloids studied were believed to be cardiac depressants and to exert their effects by acting as heart-muscle poisons. It was noted that quinin and cinchonidin were able to abolish irregularities in cardiac rhythm produced in the preparation of the hearts for the experimental procedures.

Hofmann[5] found in dog and cat hearts perfused with quinidin that the most conspicuous effect was on contractility; this effect was not due to the influence of cardiac rate, as the changes in rate were small. He believed it to be a direct effect of the poison on the cardiac muscle. Excitability was also greatly diminished, so that the threshold of stimulation necessary to produce extrasystoles or fibrillation of the auricle rose. Finally, it became impossible to bring about fibrillation.

Boden and Neukirch[6] by perfusion experiments on isolated rabbit and fetal human hearts found a marked depression of stimulus production which was manifested by bradycardia and slowing of artificially produced tachycardia. They like Hofmann found that a heart perfused with sufficient concentration of quinidin could not be made to fibrillate, or if fibrillation were already present it was abolished by the drug. Quinidin also caused a decrease in the strength of contraction of the auricles and ventricles. The coronary arteries were found to be widened by perfusion with quinidin. Hedbom[7] had previously found that quinin caused increased blood-flow through the heart, but at the same time decrease in strength of contractions.

Schott[8] made electrocardiographic studies of the effect of large doses of quinidin in guinea-pigs. He found progressive decrease of auricular rate, shallower and broader *P*-waves, marked alterations in the ventricular complex and increase in the conduction time going on to a high-grade incomplete heart-block with as many as five auricular contractions to one ventricular. Ordinarily complete dissociation would have developed instead of such a high-grade incomplete block, but Schott explains the failure of the ventricle to develop an independent rhythm on the ground that stimulus production was depressed in the lower levels of the heart as well as the higher by quinidin. But it would appear from electrocardiograms published by Boden and Neukirch[9] that the auriculoventricular node, at any rate, is able to assert itself as pacemaker for the

[5] Ztschr. f. Biol., 1920, **71**, 71.
[6] Deutsch. Arch. f. klin. Med., 1921, **136**, 181.
[7] Skand. Arch. f. Physiol., 1899, **9**, 1.
[8] Deutsch. Arch. f. klin. Med., 1920, **134**, 208.
[9] Loc. cit.

ventricles under the influence of quinidin. In some tracings there was no evidence of the spread of an excitation wave through the auricles. There were marked changes in the form of the ventricular complexes.

In studying the effects of quinidin on normal persons in therapeutic doses, Frey[10] was unable to discover any depression of cardiac contractility, but he as well as Hecht and Matko[11] found a flattening of the *T*-waves in electrocardiograms. Boden and Neukirch[12] found no electrocardiographic changes when the drug was given to normal persons. It is possible that the diversity of findings may be due to differences in administration of the drug. The details of the experiments are not given by the writers. Boden and Neukirch found no changes in urine output nor cardiac rate in normals unless the drug was given intravenously, when there was a slight increase of rate for a short time.

Weichman[13] studied the urinary excretion of quinidin. He found that excretion began quickly and was greatest during the first twenty-four hours. Smaller amounts were excreted during the next two days. With increase of urine output the excretion of quinidin was also increased. It was not affected by the administration of digitalis but apparently was increased by muscular activity of the patient. Fractionation of doses also favored rapidity of excretion. Quinidin sulphate was excreted more rapidly than quinidin, probably on account of the fact that the sulphate is more soluble and more easily absorbed than the pure alkaloid.

Boden and Neukirch[14] treated 12 cases of sinus tachycardia by oral or intravenous administration without result. They believed that a favorable effect was obtained in extrasystoles, but, as they point out, extrasystolic arrhythmia is so changeable that it is difficult to judge the results of treatment. In 6 cases of paroxysmal auriculoventricular and ventricular tachycardia the attacks were terminated in 4 and the rate decreased in 2 by intravenous injection.

It is in auricular fibrillation and flutter that the effects of the drug have been most striking. In 147 cases collected from various European sources, 4 reported by Levy[15] in this country and 12 from our clinic, 163 in all, the normal rhythm was restored in 83, a percentage of 51.5. Frey,[16] who has had the largest experience, has reported and analyzed his results in 50 cases. Of the 50 cases a normal rhythm was restored in 21, fibrillation was converted to flutter in 6 and 23 remained uninfluenced. Neither the age of the patient nor the type of cardiac disease, including the presence or absence of valve lesions, seemed to influence the results. On the

[10] Deutsch. Arch. f. klin. Med., 1921, **136**, 70.
[11] Quoted from Frey: Deutsch. Arch. f. klin. Med., 1921, **136**, 70.
[12] Loc. cit.
[13] Inaugural Dissertation, Kiel, 1918.
[14] Loc. cit.
[15] Jour. Am. Med. Assn., 1921, **76**, 1289.
[16] Loc. cit.

other hand, patients with decompensation did not react nearly so well as those whose function was less impaired. The duration of fibrillation was also found to be of importance. Those who had fibrillated only a short time reacted well, only 8 out of 24 remaining uninfluenced as compared with 13 out of 19 among those who were known to have had fibrillation for over a year. Fibrillation in thyroid disease was also found to be refractory to quinidin.

The duration of normal rhythm following its restoration by quinidin for the most part has been merely temporary. Many patients have reverted to fibrillation after a few days or weeks, although 1 patient of Boden and Neukirch's[17] at the time their paper was written had retained a normal rhythm for nine months. In Frey's[18] experience two-thirds of the patients retained a normal rhythm for at least a month. He believes that the more or less continuous administration of small amounts of quinidin tend to prevent, in a measure, the recurrence of fibrillation.

The reports on the effects of quinidin on subjective symptoms and cardiac decompensation have been somewhat conflicting. Frey has stated that the drug exerts no favorable influence on passive congestion or diuresis, in spite of the fact that the rhythm may return to normal and the patients feel better. Von Bergmann,[19] on the other hand, considered the drug life-saving in a patient with severe decompensation who was not benefited by digitalis. Under quinidin the rhythm was restored to normal and the severe decompensation and passive congestion disappeared. Leschke and Ohm[20] report that not only does quinidin bring about a restoration of the normal rhythm but improvement in the mechanical power of the heart. They give the details of one case in which passive congestion improved and exhibit venous pulse curves which they regard as evidencing cardiac improvement.

Electrocardiographic studies during the course of treatment have shown graphically the profound effect of the drug in flutter and fibrillation. Even in the cases in which fibrillation was not abolished the oscillations due to the spread of the excitation wave in the auricle tended to become less rapid and larger. In a number of cases it was observed that fibrillation was converted first either to pure flutter or to what appeared to be a transition stage between fibrillation and flutter, and then to normal rhythm. Frey noted that the *T*-wave might become less high, the *P*-waves altered in shape and conduction time increased over the normal, following the restoration of sinus rhythm. Boden and Neukirch noted prolongation of the *P–R* interval in 2 cases. On the other hand, von Bergmann found no alterations in conduction nor in the *T*-waves. A number of observers have commented on the fact that auricular extrasystoles are often found shortly after the restoration

[17] Loc. cit.
[18] Loc. cit.
[19] München. med. Wchnschr., 1919, **66**, 705.
[20] Ibid., 1921, **68**, 65.

of sinus rhythm. Von Bergmann believes that further treatment with quinidin tends to abolish them.

In a number of cases there have been untoward results. Benjamin and von Kapf[21] report two deaths that were due apparently to quinidin. One patient was decompensated with a pulse-rate of 80 to 100. Under quinidin therapy the pulse rose rapidly to 160 and the patient died of cardiac failure. In the second case, a few hours after the restoration of normal rhythm, there was sudden cardiac arrest followed about ten minutes later by respiratory failure and death. The dosage given was small. In a third case there was a lung infarct after the restoration of normal rhythm. This the authors regard as due to the improved circulation whipping a thrombus from the heart to the pulmonary artery. The patient recovered. Frey states that in some cases he saw alarming symptoms which he regarded as due to hypersusceptibility to quinidin. Such symptoms as nausea, vomiting, epigastric discomfort and pain, dizziness, fainting and even temporary arrest of respiration have been reported. Frequently the ventricular rate has increased in an alarming manner, especially in auricular flutter, where slowing of the auricular rate in some unexplained way seemed to bring about a degree of "unblocking." The explanation of this phenomenon is at present obscure, especially in view of the fact that there is evidence to indicate that quinidin depresses auriculoventricular conduction.

Report of Cases. CASE I.—J. G., white, male, aged fifty-five years. Diagnosis: Chronic myocardial disease; auricular fibrillation; cardiac decompensation; arteriosclerosis. Symptoms referable to the heart for three years, worse recently. Dyspnea, weakness, precordial pain, palpitation, swollen legs. History of excessive alcoholism. Examination showed wide aortic arch, large heart with transverse measurement of 16 cm., auricular fibrillation with ventricular rate about 90. Systolic murmur at the apex. Free fluid in the abdomen.

He received digitalis for about ten days, with moderate improvement, and was then given quinidin sulphate, 0.2 gram b. d., for one day followed by 0.4 gram t. i. d., the dose being gradually increased to 0.8 gram five times a day over a period of ten days. At this time he complained of stuffiness of the ears and slight deafness, so the drug was discontinued. The normal rhythm was not restored, nor was there any apparent effect on the cardiac rate. The patient thought he felt a little better while taking quinidin, but there was no significant change noted in his condition.

CASE II.—H. S., white, male, aged thirty years. Diagnosis: Multiple serositis, with abdominal, pleural and pericardial effusions;

[21] Deutsch. med. Wchnschr., 1921, **42**, 10.

chronic myocardial disease; auricular fibrillation. Well until five years ago, when he had attacks of dyspnea, dizziness and unconsciousness. One year ago had abdominal swelling and edema of the legs. Three months ago the abdomen was tapped and 7000 cc fluid removed. On admission there was a large area of precordial dulness and pericardial friction sounds. Total arrhythmia with ventricular rate of 75. Signs of a great deal of fluid in the abdomen and also fluid in the right chest. Teleroentgenogram showed a very large heart shadow and evidences of pericardial fluid.

After seventeen days' treatment with moderate-sized doses of digitalis the cardiac rhythm became regular and for several days there was sinus rhythm with *P*-wave in the electrocardiogram and a well-defined wave in the jugular tracing. Fibrillation was then reëstablished. About a week later quinidin sulphate was given, first two small preliminary doses then 0.4 gram t. i. d. for four days and 0.6 gram for two days. At this point in the treatment the patient left the hospital. The fibrillation was unaffected, no change was observed in his general condition and no disagreeable symptoms were noted as a result of the quinidin.

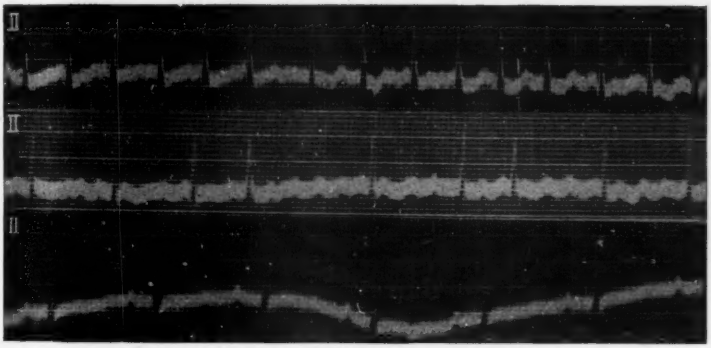

FIG. 1 (Case 3).—Top tracing made July 20, 1921. Auricular fibrillation with a ventricular rate of approximately 155. Second tracing made July 26 after 10.2 grams quinidin sulphate had been taken. Fibrillation still present but ventricular rate 92 and oscillations of auricular origin coarser and less rapid. Third tracing made July 27. Sinus rhythm. Had taken 12 grams quinidin sulphate in seven days. *P–R* interval 0.22 second. All three tracings are Lead II.

CASE III.—B. T., white, female, aged forty-five years. Diagnosis: Mitral stenosis; auricular fibrillation; moderate cardiac decompensation. First seen in the Outpatient Department February 9, 1921, when the cardiac rhythm was normal. On May 25 she was found to have auricular fibrillation. Had had symptoms referable to the heart for four years, which were much worse recently. Palpitation, precordial pain, dyspnea and hemoptysis. No history of rheumatic fever but has had syphilis. Heart markedly enlarged,

with a transverse measurement of 18 cm. Clear-cut signs of mitral stenosis. Auricular fibrillation with a ventricular rate of 100.

She was given two preliminary small doses of quinidin sulphate, followed by 0.4 gram t. i. d. for one day, when her rhythm became normal. After a few days she was discharged but was readmitted six weeks later with a history that she had felt well for two weeks after leaving the hospital, but since then had been worse than before. Again there was fibrillation, this time with a ventricular rate of about 130. Received quinidin sulphate, 0.4 gram t. i. d. for five days and 0.6 gram t. i. d. for three days, when the normal rhythm was again restored. During the first four days of quinidin therapy the rate became more rapid and was counted as high as 155. It then fell to below 100 and the auricular oscillations in the electrocardiogram became larger, more nearly uniform and regular and less rapid, somewhat resembling flutter. After the restoration of sinus rhythm she was given quinidin sulphate, 0.2 gram b. d., and began to improve rapidly. Five weeks later the rhythm was still normal and she felt well. Two weeks after this she was seen again—was feeling worse and was again fibrillating. No disagreeable effects were noted from quinidin.

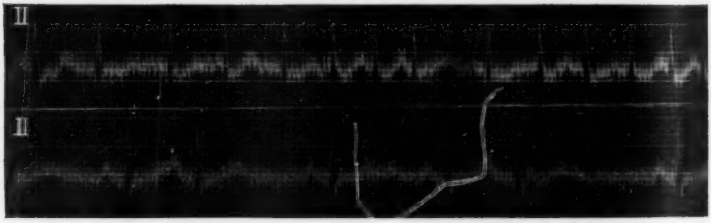

FIG. 2 (Case 4).—Upper tracing made July 5, 1921. Auricular fibrillation, ventricular rate about 150, constantly varying form of ventricular complexes. Lower tracing made July 6 after having received 1.6 grams quinidin sulphate. Normal type of rhythm. *P–R* interval 0.20 second. Both tracings are Lead II.

CASE IV.—E. W., white, female, aged fifty-eight years. Diagnosis: Adenoma of the thyroid; syphilis; chronic myocardial disease; auricular fibrillation. Has had swelling of the neck for seven years. Moderately nervous. No exophthalmos. Heart enlarged; transverse measurement, 16 cm. No evidence of valvular disease. Ventricular action rapid and irregular; a few rales at the bases of the lungs; liver enlarged; moderate edema of the legs. Basal metabolism, 37.7 per cent above the normal. Electrocardiogram showed auricular fibrillation, with a ventricular rate around 150.

Received preliminary doses of quinidin sulphate, 0.2 gram b. d. followed by 0.4 gram t. i. d. for one day. The next morning the rhythm was normal and the rate 84. She was then given 0.2 gram

b.d. for three weeks, the rhythm remaining normal while the cardiac function improved remarkably. Her son reported a month later that her improvement had continued. No disagreeable effects were noted as due to the quinidin.

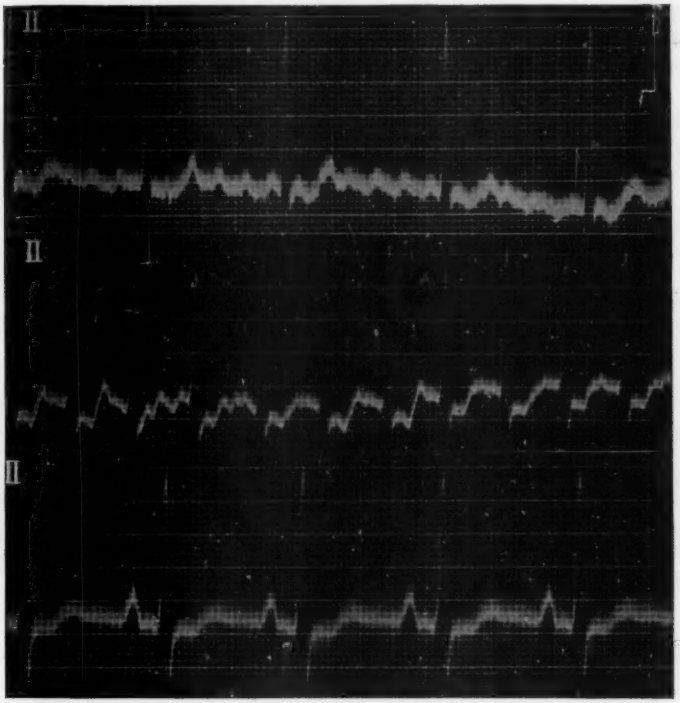

FIG. 3 (Case 5).—Top tracing made June 27, 1921, after 6.2 grams quinidin sulphate had been taken in five days. Fibrillation still present with ventricular rate averaging 65. Second tracing made June 29 after 9.8 grams quinidin. Ventricular rate 155 and nearly regular. Probably impure flutter. Third tracing made July 1 after 13.8 grams quinidin. Sinus rhythm restored with rate of 71. *P–R* interval 0.21 second. All tracings are Lead II.

CASE V.—C. N., white, female, aged twenty years. Diagnosis: Mitral stenosis and regurgitation; auricular fibrillation. Under observation constantly since 1919 and has had auricular fibrillation continuously for over two years. The heart is very large and the signs of mitral disease clear-cut. Two attacks of rheumatic fever. Does well on digitalis but quickly becomes severely decompensated if she neglects treatment. Was fairly well-compensated when she was sent to the hospital for quinidin.

Received quinidin sulphate: First day 0.2 gram b. d., then 0.4 gram t. i. d., the dose being gradually increased to 0.6 gram q. i. d.

over a period of eight days, when her rhythm became normal. After six days' treatment the ventricular rate jumped to 155, but she felt no worse at this time. After the restoration of normal rhythm she received 0.2 gram b. d. and was sent home. At this time she said she had less palpitation than usual, but otherwise felt no better. When she reported two weeks later she was again fibrillating. No disagreeable subjective symptoms were noted as due to quinidin.

FIG. 4 (Case 6).—Top tracing made July 8, 1921. Auricular fibrillation. Had taken no drugs for several weeks. Second tracing made July 11 after 2.8 grams quinidin sulphate. Sinus rhythm. *P–R* interval 0.3 to 0.32 second. Third tracing made September 7. Had been receiving 0.4 gram quinidin daily. *P–R* time 0.23 second. Marked increase in height of *T*-wave. All tracings are Lead II.

CASE VI.—B. K., white, male, aged fifty years. Diagnosis: Aortic regurgitation and auricular fibrillation. Well until six months ago, when he began to suffer from digestive symptoms. Slight cardiac palpitation and marked dyspnea on exertion. Unable to do much work. Heart only moderately enlarged. Auricular fibrillation of the slow type.

Treated with digitalis for about a month without improvement. Was given quinidin sulphate 0.2 gram b. d. for one day followed by 0.4 gram t. i. d. for two days, when the rhythm became normal. Continued to take 0.2 gram b. d. There has been no recurrence of fibrillation in over two months. Has steadily improved; has no symptoms except on exertion and is able to work all day as a clothes-presser and tailor. During the first week of quinidin therapy even small doses caused epigastric distress, but later the drug was well tolerated.

CASE VII.—L. C., white, male, aged forty-seven years. Diagnosis: Hyperthyroidism, chronic myocardial disease and auricular fibrillation. Had been under observation for about one year on account of hyperthyroidism and cardiac condition, which was considered secondary to the thyroid disease. Treated by roentgen ray, with marked clinical improvement and fall in the metabolic rate. Had received digitalis therapy a number of times without much effect on his cardiac condition.

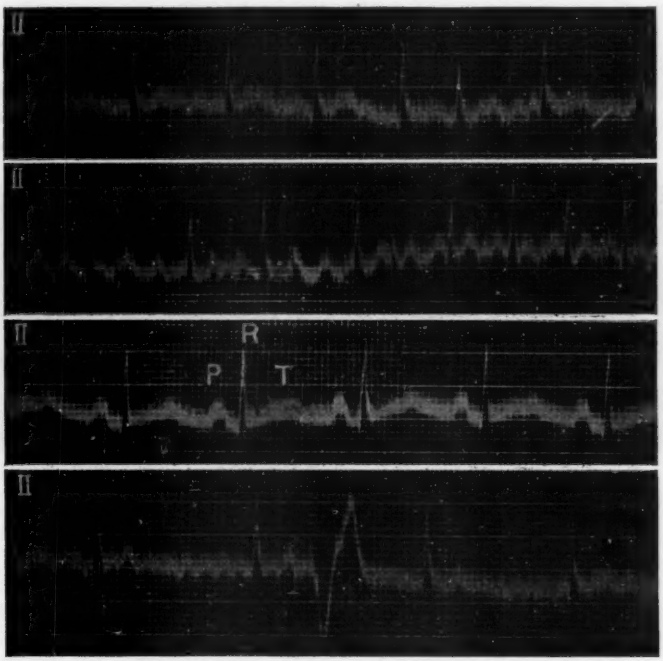

FIG. 5 (Case 7).—Top tracing made June 20, 1921. Auricular fibrillation, ventricular rate 110. Second tracing made June 22 after 2 grams quinidin sulphate. Auricular oscillations larger and less rapid. Third tracing made June 27 after 13.6 grams quinidin sulphate. Sinus rhythm, *P–R* interval 0.18 second. Fourth tracing made July 7. Auricular fibrillation. All tracings are Lead II.

He was given quinidin sulphate, 0.2 gram b. d. for one day, 0.4 gram t. i. d. for two days and 0.6 gram t. i. d. for six days, when the rhythm became normal. He was then discharged and ordered 0.2 gram b. d., which he did not take. When he reported the next week he was fibrillating again.

Two days before the restoration of normal rhythm the ventricular rate became quite rapid and the electrocardiographic auricular

oscillations larger, slower and almost uniform, approaching the type of tracing found in flutter. No disagreeable symptoms were noted from taking quinidin.

CASE VIII.—E. P., white, female, aged forty-two years. Diagnosis: Chronic myocardial disease, auricular fibrillation and cardiac decompensation. Shortness of breath and cardiac palpitation for several months; worse recently. Heart greatly enlarged; auricular fibrillation with ventricular rate of 160.

Received quinidin sulphate 0.2 gram b. d. for one day and 0.4 gram t. i. d. for one day, when the rhythm became normal and the rate dropped from 160 to 70. Continued to take 0.2 gram b. d. Discharged eight days later with normal rhythm. Readmitted after five weeks with fibrillation again. She had felt better for several weeks after leaving, but recently was worse again. Given

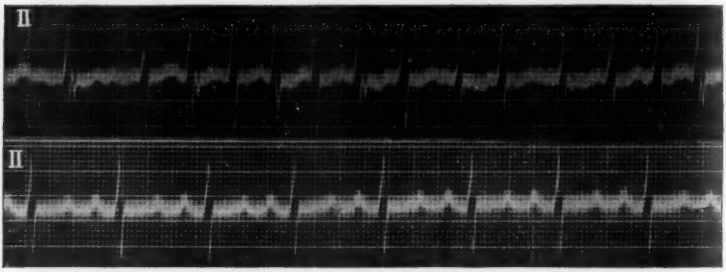

FIG. 6 (Case 8).—Upper tracing made July 2, 1921. Auricular fibrillation, ventricular rate 155. Lower tracing made July 5, 1921. Had received 2.8 grams quinidin sulphate. Sinus rhythm with auricular extrasystoles. Rate of dominant rhythm 68. Both tracings are Lead II.

0.4 gram quinidin sulphate t. i. d. and the dose gradually increased to 0.6 gram q. i. d. over a period of twelve days without interrupting the fibrillation. After three days without quinidin it was again given in dosage of 1 gram t. i. d. and the normal rhythm was restored in one day. During the entire period she received also 1 cc tincture of digitalis t. i. d. The rhythm remained normal for about a week and then reverted to fibrillation again in spite of the fact that she was taking 0.2 gram quinidin sulphate b. d. During the time the largest doses of quinidin were given she complained of feeling weak and dizzy.

CASE IX.—J. C., white, male, aged fifty-three years. Diagnosis: Chronic myocardial disease and auricular fibrillation. Well until six months ago, when he began to have digestive disturbances. His physician diagnosed heart disease. Came to the cardiac clinic with severe decompensation and auricular fibrillation with very rapid

ventricular rate, and was immediately referred to the ward. He improved markedly on rest and digitalis therapy and the evidences of passive congestion disappeared. Was then given quinidin sulphate, 0.2 gram b. d. for one day, 0.4 gram for five days and 0.6 gram for one day, when his rhythm became normal. Then received 0.3 gram for five days, when fibrillation recurred, but was restored to normal again by 0.6 gram t. i. d. for two days. The dosage was then tapered down to 0.2 gram b. d. and digitan 0.03 gram t. i. d. was also given. Ten weeks after discharge the rhythm was still normal; he had regained a considerable degree of compensation and was able to walk long distances and climb stairs without distress. He felt better immediately after the interruption of fibrillation both times. The most striking thing to him was the disappearance of palpitation. No disagreeable effects were noted from the quinidin.

Case X.—R. R., white, female, aged twenty-five years. Diagnosis: Mitral stenosis, auricular fibrillation. Had been under observation for about two years in the Pennsylvania Hospital Medical Dispensary. The fibrillation had been present all that time. Responded well to digitalis. Became pregnant and shortly before term was sent to the University Hospital Maternity for delivery. She was kept well digitalized and Caesarean section was performed without any cardiac embarrassment. One week later quinidin sulphate was begun, 0.2 gram b.d. followed by 0.4 gram t. i. d. for eight days, without any noticeable effect on the fibrillation. There were no disagreeable effects ascribable to quinidin.

Case XI.—M. M., white, female, aged fifty-one years. Diagnosis: Chronic myocardial disease and auricular fibrillation. Cardiac symptoms for twenty months. On admission she was severely decompensated with edema of the back and legs, congested pulmonary bases, enlarged liver and ascites. Heart markedly enlarged with transverse measurement of 17 cm. Loud systolic murmur at the apex. Auricular fibrillation with very rapid ventricular rate. There was a slight improvement after ten days' rest in bed and digitalis therapy. She then received quinidin sulphate 0.2 gram b. d. the first day, 0.4 gram t. i. d. for six days and q. i. d. for five days. At the same time 3 cc digalen was given daily by hypodermic. The fibrillation was not interrupted. After three days' intermission she was given 1 gram quinidin sulphate t. i. d. for three days, again without interrupting the fibrillation. No disagreeable effects were noted from the quinidin.

Case XII.—G. H., white, male, aged twenty-four years. Diagnosis: Aortic and mitral regurgitation; auricular fibrillation; moderate cardiac decompensation. Said to have had valvular heart disease since the age of eight, when he had diphtheria. At

fifteen had some shortness of breath. About three months ago it was noticed that he had "extra beats" of his heart. Up to then he had done heavy work but since has grown rapidly worse. Heart greatly enlarged; clear-cut signs of mitral and aortic regurgitation; auricular fibrillation with ventricular rate of about 150. Moderate orthopnea; no passive congestion.

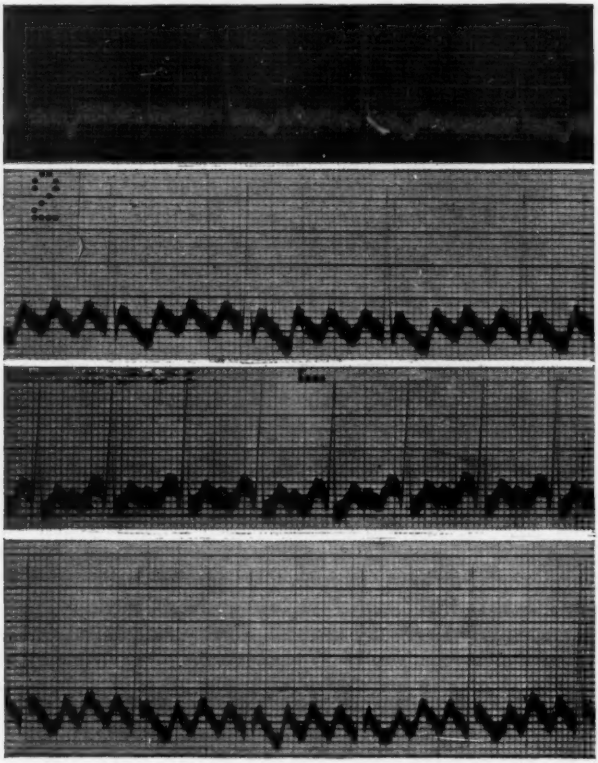

FIG. 7 (Case 12).—Top tracing made September 30, 1921. Auricular fibrillation with slow ventricular rate. Second tracing made October 3 after 2.4 grams quinidin sulphate had been taken. Auricular flutter four to one block, auricular rate, 271. Third tracing made October 6 after 6 grams quinidin sulphate. Auricular flutter two to one block, auricular rate 245. Fourth tracing made October 13, 1921, after withdrawal of quinidin for five days and substitution of digitalis. Auricular flutter four to one block, auricular rate, 316. All tracings are Lead II.

He received quinidin sulphate—the first day 0.2 gram b. d. and then 0.4 gram t. i. d.—which was increased to 0.8 gram t. i. d. in five days, when it was stopped because of ringing in the ears. The ventricular rate had dropped to around 95 and the patient stated

that he felt much better. Five days later quinidin was again given, 0.4 gram t. i. d. On the third morning of this treatment a regular four to one flutter developed. After the dosage was increased to 0.6 gram t. i. d. the auricular rate became slower, but on account of the development of a two to one block the ventricular rate was much more rapid. With the rapid ventricular rate dyspnea quickly ensued and the treatment had to be discontinued. Ten days later fibrillation was reëstablished.

Discussion. Of the 12 cases of auricular fibrillation treated with quinidin the normal rhythm was restored in 7, the fibrillation converted to flutter in 1, while in 4 the treatment failed to abolish the fibrillation. In the last group the dosage was probably inadequate in 2 cases (Cases II and X), but in the other 2 it was increased to the point where symptoms due to the drug appeared. It is of some interest that in 1 of the cases in which quinidin was not successful (Case II) there had been a period of normal rhythm a short time previously during the administration of digitalis.

In 2 cases (Cases V and VII) there was no clinical benefit from the restoration of normal rhythm, as the fibrillation was reëstablished within two weeks. In two others (Case III and VIII) the results might be regarded as moderately successful. Fibrillation was abolished for periods of several weeks and the patients stated that they felt better during that time. But in both fibrillation returned and was much more refractory to a second course of treatment, although it was again possible to restore sinus rhythm temporarily.

In 3 cases (Cases IV, VI and IX) the results of quinidin therapy were excellent. Case VI had been thoroughly treated by digitalis through at least two prolonged courses of treatment without much benefit. His fibrillation was easily abolished by quinidin and his rhythm has remained normal for a period of more than two months. There has been striking clinical improvement. Case XI had been severely decompensated but had improved somewhat under digitalis. There was a further very distinct improvement after the restoration of normal rhythm by quinidin. His normal rhythm has now remained for nearly three months, during which time there has been a steady improvement in cardiac strength. Case IV showed the most striking effect of all. From one day's treatment the heart action changed from fibrillation, with a ventricular rate of 150, to normal rhythm, with a rate of 88. It is noteworthy that her cardiac condition had probably been due to hyperthyroidism, a type that Frey found especially refractory to treatment.

During the periods that attempts were being made to abolish fibrillation the subjective effects were various. Four patients, including 2 in whom the treatment was unsuccessful, said they felt better, but in the remainder there was no improvement. One complained of weakness and dizziness, 1 of epigastric distress,

1 of a sensation of stuffiness in his ears and slight deafness and 1 of ringing in his ears. No visual disturbances were complained of. In no case did alarming symptoms develop. Several patients who were annoyed by perception of their heart action were either entirely relieved of this symptom or much benefited during the time the rhythm was normal.

There was no significant effect noted on urinary excretion either in the direction of increasing or diminishing the output. Even after the return of normal rhythm there was no particular change, although it should be said that none of the patients had much edema at the time quinidin was being given.

In 3 patients there was rather sudden marked increase in ventricular rate, which was considered an effect of quinidin. In 1 of the 3 symptoms of cardiac embarrassment quickly began to develop and the drug was discontinued, but in the other 2 the rapid rate was well tolerated and in both normal rhythm was soon established.

In Figs. 1, 3 and 5 are seen effects of quinidin on the auricular waves of the electrocardiogram during fibrillation. The oscillations tend to become larger, less rapid, more nearly uniform, somewhat approaching in form the curves of flutter. In only one case was pure flutter observed (Fig. 7). From such evidence it would seem that quinidin must exert a profound effect on the transmission of the excitation wave through its abnormal path in non-specialized auricular muscle. It seems not unlikely that such an effect of the drug may play an important part in the abolition of fibrillation and flutter.

After the restoration of normal rhythm in our cases the auriculoventricular conduction time appeared to be increased above the average. In only 2 was the *P–R* time as short as 0.18 second, In 2 others it was about 0.2 second while in 3 it was 0.21 second or more. One patient (Case VI) received only a small amount of quinidin but the *P–R* interval was 0.3 to 0.32 second shortly after the restoration of normal rhythm, while another (Case IX) took large amounts of quinidin without increasing the *P–R* interval above the normal limit. It is therefore scarcely justifiable to assume that the alterations in conduction from the normal that were observed are necessarily due to quinidin.

The presence or absence of valvular disease, so far as can be judged from this small series, did not appear to affect the efficacy of the treatment. Of the 5 cases with valvular disease 3 had the normal rhythm restored as compared with 4 successful cases out of 7 without valvular disease. Likewise the age of the patient did not seem to make any particular difference. The normal rhythm apparently is not more nor less difficult to restore in the elderly than in the young.

Treatment. The use of quinidin in the treatment of auricular flutter and fibrillation is, to a certain extent, in an experimental

stage, but certain points in respect of the types of cases in which the drug may be employed and details of treatment have been established.

The most favorable cases for treatment are those with (1) relatively good heart muscle and at least fair compensation, and (2) flutter or fibrillation that has been present only a short time.

In cases with good heart muscle the restoration of sinus rhythm with the abolition of the mechanical disadvantage to the heart of such profound disturbances of its mechanism, as fibrillation or flutter may be expected to yield good results. But the use of the drug in patients with weak heart muscle is not so likely to be beneficial. Not only is it dangerous to use so depressant a drug as quinidin in such cases, but the chance of restoring the normal rhythm is much less. It is doubtful whether the advantages that may be gained by the restoration of normal rhythm in a comparatively low percentage of cases in this group counterbalances the disadvantage of still further disturbing the compensation in some cases and the possibility of meeting disaster.

The importance of the duration of flutter or fibrillation has been mentioned. It is agreed by most observers that if the abnormal rhythm is of recent origin it is much more easily removed. Not only may a small amount of quinidin be sufficient to restore the normal rhythm, but apparently the recurrence of fibrillation is more easily prevented in these cases.

In the management of patients under quinidin therapy a close observation should be maintained. The possibility of the rapid development of alarming symptoms makes it necessary that immediate attention be available. Consequently the patient would better be in a hospital or under the care of a well-trained nurse. On account of the abrupt changes in the cardiac mechanism it is a decided advantage to make frequent electrocardiographic examinations.

The sulphate of quinidin has been found preferable to the pure alkaloid in treatment on account of the insolubility of the latter. Thus far the drug has usually been given by mouth. Because of the possibility of hypersusceptibility of the patient one or two small preliminary doses, such as 0.2 gram, should be given. If any symptoms develop from such small amounts the treatment should not be undertaken. If there is no hypersusceptibility, larger doses may be given, beginning with approximately 0.4 gram t. i. d. and gradually increasing to 1 gram t. i. d. in a person of average size. It is probably not worth while to continue a course of treatment more than ten days. After a rest period a second course may be instituted if the first is unsuccessful.

As soon as normal rhythm is discovered the large doses of quinidin should be discontinued. The problem then changes to one of maintaining the normal rhythm. Thus far the results have not

been brilliant, but this may be due in part to lack of knowledge of the proper amount of quinidin the patient should take. It has been customary not to give more than 0.2 gram b. d. A great deal of work remains to be done in this field. It would appear reasonable to avoid any strain on the heart for a long time after the restoration of normal rhythm, since a strain might be expected to help convert the mechanism back to fibrillation.

The types of disagreeable effects that may occur during quinidin administration have already been stated. In the present state of our knowledge extreme caution should be observed in giving the drug if any of them develop. Such symptoms as increasing weakness, dyspnea, dizziness or precordial distress or manifestations of cinchonism, such as ringing in the ears, deafness or stuffiness in the head, should call for withdrawal of treatment. The development of a rapid ventricular rate presents a problem. If the fibrillation has been converted to flutter or a transition stage between fibrillation and flutter it is desirable to continue the treatment if possible in spite of tachycardia, since the prospect of the return of normal rhythm is good. But if symptoms of cardiac embarrassment supervene the treatment should be discontinued. Likewise should tachycardia develop before the course of the excitation wave in the auricle has been much altered the treatment would better be stopped.

Summary. 1. Studies of the physiologic action of quinidin have shown that it is a cardiac depressant influencing chiefly the functions of contractility, excitability and conductivity.

2. Quinidin has been found effectual in restoring the normal rhythm in auricular fibrillation and flutter in slightly over one-half the cases thus far reported.

3. Observations on 12 cases of auricular fibrillation treated with quinidin are reported and the effects of treatment discussed.

4. Quinidin therapy is still in the experimental stage. If it is used there must be careful selection of cases and constant observation during the course of treatment.

NON-SPECIFIC WASSERMANN REACTIONS IN DIABETES MELLITUS.

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In a series of 168 cases of diabetes mellitus treated in this clinic during the last four years, 2 cases have been observed which gave strongly positive Wassermann reactions upon their blood, there

being no history or other signs or symptoms of a specific infection. Both cases were treated for their supposed syphilitic infection over a short period of time, with marked and rapid decline of their carbohydrate tolerance. This effect upon their carbohydrate tolerance was so striking that it seemed to justify a report.

SERIAL CASE I.—Case No. 27672. Male, aged five years. Weight, 15 kilos. First admission April 11, 1918. First symptom of polyuria about February 1, 1918. Glucose was first found in the urine March 15, 1918. There was no loss of weight; no history of head injury; and the heredity was negative. There had been no previous treatment. Physical examination was negative. Treatment was instituted and the patient was discharged on June 21, 1918, with an intake of protein, 60 grams; fat, 70 grams; carbohydrate, 70 grams; giving 4 grams of protein with 73 calories per kilo body weight. Weight on discharge was 14.8 kilos. There was no acidosis and the fasting blood sugar ranged from 0.07 to 0.08 per cent.

Subsequent to discharge the patient remained almost continually free from glycosuria until September, 1919. During this time his intake was protein, 60 grams; fat, 69 grams; carbohydrate, 70 grams; and his weight had increased to 19.9 kilos.

Due to the breaking of his diet he was readmitted on October 1, 1919, with marked acidosis and a greatly lowered carbohydrate tolerance. A Wassermann upon his blood was positive (++++) on November 1 and 11, 1919. These were both fasting bloods; there was no lipemia and the reactions were performed with both human and guinea-pig complement-fixation taking place both at 37° C. and at 5° C. The family history was negative. Blood Wassermanns upon both parents were negative. The patient was given intravenously 0.15 gram and 0.4 gram of neophenarsenyl (manufactured by Phenarsenyl Company, Montreal, Canada) on November 18, 1919, and November 25, 1919, respectively, without reactions. Blood Wassermann upon November 29, 1919, was negative. A further injection of 0.45 gram of neophenarsenyl was given on December 3, 1919.

Table I shows the course of this patient's treatment while in the hospital, with the effect of the specific treatment upon the carbohydrate tolerance:

Subsequently at home during the first week after discharge he had glycosuria on an intake of protein, 15 grams; fat, 10 grams; carbohydrate, 10 grams. By January 27, 1920, his tolerance had increased to protein, 30 grams; fat, 18 grams; carbohydrate, 15 grams without glycosuria. Subsequently glycosuria appeared at more frequent intervals, with a marked decrease in the carbohydrate tolerance, death following on March 23, 1920. There was no terminal coma.

TABLE I.—ALL BLOOD SUGARS WERE DONE BY THE LEWIS-BENEDICT TECHNIC.

Date, 1919.	Intake.			Glycosuria, grams.	Blood.		Weight, kilos.	Neophenarsenyl, grams.
	Protein, grams.	Fat, grams.	CHO, grams.		Sugar, per cent.	CO_2 vols., per cent.		
Oct. 2	7.5	1.3	60.0	54.0	0.402	36.1	19.18	
8	6.0	1.0	24.0	14.4	.....	....	19.09	
9	Fast day		....	0.0	0.360	50.0	19.54	
12	5.4	1.0	15.0	0.0	.....	....	20.90	
24	20.0	1.0	15.0	0.0	0.194	....	17.72	
Nov. 3	30.0	20.9	25.0	0.0	0.174	....	16.25	
14	40.0	20.5	30.0	0.0	0.197	....	16.37	
18	40.0	25.1	30.0	0.0	0.190	....	17.37	0.15
24	40.0	30.7	40.0	0.0	0.211	....	17.37	
25	40.0	30.7	40.0	3.69	.....	....	17.37	0.40
26	40.0	30.7	40.0	9.01	.....	....	17.37	
Dec. 1	40.0	30.0	35.0	3.36	.....	....	16.92	
2	40.0	30.0	35.0	8.00	.....	....	16.81	
3	40.0	30.0	35.0	7.42	0.272	....	16.81	0.45
5	40.0	30.0	35.0	8.12	.....	....	16.59	
6	Fast day		....	0.0	.....	....	16.59	
7	Discharged							

A summary of the more important fasting blood sugars showing the increasing hyperglycemia after the neophenarsenyl follows:

TABLE II.

Date, 1919.	Blood sugar, per cent.	Remarks.
Oct. 2	0.402	With glycosuria.
9	0.306	First day free from glycosuria.
16	0.288	No glycosuria.
Nov. 10	0.163	No glycosuria.
18	.....	Neophenarsenyl, 0.15 gram.
20	0.192	No glycosuria.
24	0.211	No glycosuria.
25	.....	Neophenarsenyl, 0.40 gram.
27	0.277	No glycosuria.
Dec. 3	.....	Neophenarsenyl, 0.45 gram.
4	0.272	Slight glycosuria.

Nitrogen studies show an inability on the part of the patient to maintain a nitrogen equilibrium both before the neophenarsenyl with an intake of 22.8 calories per kilo and after its injection when receiving 32 calories per kilo. During both of these periods the grams of protein per kilo body weight were practically the same. With the latter period there was almost the same loss of nitrogen per day, 1.48 grams as against 1.14 grams for the former period. This shows that the nitrogen metabolism was greatly stimulated subsequently to the neophenarsenyl administration, the patient needing an increased supply of calories.

SERIAL CASE II.—Case No. 31112. Female, aged nineteen years. Admitted October 2, 1919, complaining of weakness. Was quite well until February, 1919, when she noticed increased thirst. Glucose was first found in the urine in April, 1919. Since May, 1919, she had lived upon a restricted carbohydrate diet. No history of head injury. One aunt on her mother's side died of diabetes at the age of thirteen years. Physical examination was negative except for a pruritus vulvæ.

Upon admission the first twenty-four-hour glycosuria was 52 grams upon an intake of protein, 82 grams; fat, 80 grams; carbohydrate, 128 grams. There was a slight acidosis. No blood sugar was done until October 6, the first day free from glycosuria, when it was 0.228 per cent. Under treatment the glycosuria rapidly disappeared, the acidosis cleared up and the fasting blood sugar fell to 0.094 per cent. By November 18, 1919, her tolerance had been built up to protein, 75 grams; fat, 80 grams; carbohydrate, 110 grams, without glycosuria and with a fasting blood sugar of 0.17 per cent.

On November 1, 1919, a blood Wassermann was four plus (++++). Repeated on November 11, 1919, it was the same with both human and guinea-pig complement-fixation taking place both at 37° C. and at 5° C. Both of these bloods were fasting specimens and there was no lipemia. The personal and family histories were negative. On November 18, 1919, she was given 0.15 gram of neophenarsenyl intravenously. A second injection of 0.55 gram was given on November 25, 1919. On November 27, 1919, the blood Wassermann was negative. No further treatment was given.

In Table III is tabulated the reaction of the specific treatment upon the carbohydrate tolerance:

TABLE III.

Date. 1919.	Intake.			Glycosuria, grams.	Blood sugar, per cent.	Weight, kilos.	Neophenarsenyl. grams.
	Protein. grams.	Fat, grams.	CHO, grams.				
Nov. 10	75	70	90	0	0.130	44.31	
13	75	70	100	0	0.170	44.09	
17	75	80	100	0	0.180	44.09	
18	75	80	110	0	.....	44.09	0.15
19	75	90	110	0	.....	44.09	
20	75	90	110	0	0.166	44.09	
21	85	90	110	7.13	.....	44.09	
22	85	90	110	9.45			
23	43	45	55	0			
24	75	90	110	0	0.210–		
25	75	90	110	4.67	.....	.....	0.55
26	75	90	110–	8.74	.....	44.54	
27	Discharged		...	....	0.208		

Subsequent to discharge the patient's tolerance dropped off very rapidly, as shown in Table IV.

TABLE IV.

Date. 1919.	Intake.			Glycosuria.
	Protein, grams.	Fat, grams.	CHO, grams.	
December . .	80	90	70	++
1920.				
January . . .	75	80	80	+
February . . .	70	80	70	+
March . . .	30	40	50	+

On March 17, 1920, she was readmitted to the ward with a tolerance as shown in Table V. Her blood Wassermann on March 23 was negative.

TABLE V.

Date. 1920.	Intake.			Glycosuria. grams.	Blood sugar, per cent.	Weight. kilos.
	Protein, grams.	Fat, grams.	CHO, grams.			
March 18	52	49.0	50.0	54.7	0.308	45.90
19	52	49.0	50.0	54.2	..	45.67
20	52	49.0	50.0	43.7	..	45.75
21	25	25.0	25.0	22.3	..	45.75
22	Fast day		....	4.9	0.258	45.22
23	20	....	....	0	..	45.76
24	20	....	....	0	..	45.00
25	25	....	....	0	0.170	45.00
26	40	0.5	10.0	0	..	44.54
27	50	0.8	15.0	0	..	44.22
28	60	0.7	20.0	0	..	44.76
29	60	10.9	20.0	3.36	0.200	44.76
30	20 (Breakfast only)	3.5	8.9	0		

Since her second discharge from the hospital, on March 31, 1920, her tolerance has still remained very low. Most of the time she has continued to have glycosuria and the diet has not been so strictly controlled as before.

Discussion. The occurrence of these strongly positive Wassermann reactions in cases of diabetes mellitus where there is no history or evidence of a past infection must be considered conservatively. Why they should have become negative so promptly with only slight treatment is difficult to explain, as it would appear that the reactions

were due to some disturbed physico-chemical relationship, which two injections of neophenarsenyl one would not expect to influence.

Working with the sera from known cases of diabetes mellitus, Van Saun[1] came to the conclusion that "with carefully controlled tests non-specific fixations can always be checked." Likewise Williams[2] is willing to state there is no danger of obtaining non-specific reactions.

The reported facts would indicate that material damage was done to the patients by the arsenic treatment. Probably the arsenic acted as a toxic agent upon the weakened pancreatic cells, altering the quantity or nature of their internal secretion. That it acted generally upon the glucose burning cells of the body is difficult to believe, as it apparently has no effect upon the carbohydrate tolerance when administered to syphilitic patients.

LEAD POISONING, WITH SPECIAL REFERENCE TO POISONING FROM LEAD COSMETICS.

REPORT OF FOUR FATAL CASES OF ENCEPHALOPATHIA SATURNINA OCCURRING IN ONE FAMILY.

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Introduction.—The importance of lead and its compounds in producing disease is known to very few—doctors as well as laymen—in spite of the fact that, from the standpoint of industrial poisons alone, it is the most subtle and most productive of ill-health. "If a pound of lead drops on a workman's head the catastrophe is more obvious than if minute quantities of lead are taken into the system day by day, but the poisoning may be as fatal as the accident."[1] Its foremost rank among the etiologies of the occupational diseases is to be explained by the fact that it is more or less essential in about 150 industries.[2] But great as may be the extent of its use in the industries, there is another purpose for which it is perhaps even more extensively used, that of cosmetics. Its ravages in this form,

[1] Jour. Med. Research, 1917, xxxvii, 205.
[2] Jour. Am. Med. Assn., 1918, lxx, 365.

though by far less intensive, are very probably more widespread, and in the sum total cause greater unhappiness, discomfort and illness because of the fact that owing to its insidious and intangible poisonous action on the human body it remains unsuspected and unrecognized.

The fact that cases of poisoning due to lead-containing cosmetics usually remain undiagnosed, may perhaps explain why there is so little to be found in the literature relative to this type of poisoning. Oppenheim[3] makes the statement that the use of cosmetics containing lead (rouge) sometimes produces poisoning. Similarly, Rosenau[1] states that lead poisoning may be caused by the absorption through the skin from cosmetics containing lead. Lewandowsky,[4] Osler and McCrae[5] and Sollmann[6] mention the occurrence of poisoning from lead-containing cosmetics (paint, rouge, hair-dyes) as not uncommon. Cooley,[7] in 1866, stated that the daily use of oil or pomatum containing a few grains of lead carbonate or lead plaster are unsafe for long-continued use. "Atrophy of the scalp, baldness and even local paralysis have sometimes though rarely been caused by them." But none of these authors gives any details beyond these meager statements. Out of hundreds of references in the literature dealing with lead poisoning in its various phases only one was found to bear directly upon poisoning from lead-containing cosmetics, and by a remarkable coincidence the cases and conclusions bear a very close resemblance to those which form the basis of the present study.

This article, published forty years ago by J. W. Holland,[8] warns against the dangers lurking in cosmetics which are not guaranteed to be free from lead and its compounds. In the two cases cited by him, curiously enough, the cosmetic involved is identical with that which was found to be the etiological factor in the poisoning which forms the subject of this paper.

His first case is that of a seamstress, aged twenty-eight years, who presented a blue line on the gums, double wrist-drop, pale and sallow complexion and yellowish, discolored eyes. She asserted that to her knowledge she had not been exposed to lead in any form. However, a very evident application of powder on her face led to the disclosure of the fact that for two years she had made unstinted use of a fine white powder sold by druggists under the name of "Flake White." During this period she had repeatedly suffered from constipation and colic which were attributed to indigestion. She also had had spasmodic attacks of vertigo and headache. After she had used the powder for about a year she was treated by her doctor for melancholic mania. During the second year she developed weakness, tremors of the hands, and became depressed in spirits and irritable. Her doctors had been unable to diagnose her case and it was only when she had developed double wrist-drop that she consulted Holland, who made the correct diagnosis.

On her second visit she was accompanied by her younger sister, who had stopped working because of failing health and loss of power in her right hand. She had lost in weight and suffered from attacks of rheumatism in the shoulders and the right elbow. Twice her doctors had treated her for supposedly epileptic convulsions. She also admitted having used the same cosmetic during the previous two years.

Holland very aptly points out how insidious and undetected are the effects of lead cosmetics when the melancholic delirium and epileptiform convulsions were not recognized as part of the syndrome of lead encephalopathy, when lead arthralgia was treated for rheumatism, and when lead colic and constipation were regarded as merely phases of a weak digestion.

Before proceeding with the discussion of the major cases in this study it is interesting to note that among 20,000 admissions to the University Hospital, Minneapolis, there were 7 cases admitted which were diagnosed at the hospital as chronic lead poisoning. Of these 6 were men and 1 a woman. Of the 6 cases 2 were painters who had been sent to the hospital with the diagnosis of chronic lead poisoning. These had the classical signs of constipation, severe headaches, colicky pains in the region of the umbilicus and the lead lines on the gums. A third was a paint filler who was sent in with a diagnosis of diabetes mellitus and probable stone in the left kidney. A fourth was a painter sent in as a case of neuritis. A fifth, occupation not mentioned, was sent in with the diagnosis of duodenal ulcer or gallbladder disease. He presented characteristic symptoms and findings of lead poisoning, including basophilic granulations of the red cells. The sixth case, occupation not given, was sent in with the diagnosis of gastric ulcer, carcinoma or gastritis. This case also gave the symptoms and findings of lead poisoning. He had been in one of the large hospitals of the city six months previously, suffering from the same complaints that he had on entering the University Hospital—colic, vomiting, weakness, loss in weight and anemia—but the correct diagnosis had not been arrived at. Of these 6 cases only 2 had been correctly diagnosed by the physicians who referred them. Of the remaining 4 cases 2 presented symptoms and findings sufficient for a proper diagnosis. The other 2 cases were men employed in occupations which should have strongly hinted at the probable etiology of the symptoms, and yet so unknown and unsuspected are cases of lead poisoning that they went unrecognized even when the occupation alone should have been sufficiently suggestive.

REPORT OF CASES.

CASE I.—The seventh case, G. D., Hospital No. 9618, that of a woman, is almost a duplicate of the first case cited by Holland.[8] The patient, also a seamstress and of the same age, twenty-eight

years, was admitted on the service of Drs. Rowntree and Richards on September 21, 1916, complaining of pain in the epigastrium, insomnia, nervousness and pain in the arms. Her doctor sent her in with the diagnosis of an indeterminate pelvic condition. She stated that she had had attacks of severe cramp-like pains in the epigastrium, accompanied by nausea and vomiting, for about ten years. These attacks would last about two weeks and recurred two or three times a year. Nothing seemed to relieve the pain.

During the three months previous to her admission the symptoms of weakness, nervousness, dyspnea, loss of weight, constipation, abdominal cramps and vomiting became so severe that she had to quit her work. She also developed pains in her arms. She stated that she had had two operations: one for appendicitis, seven years ago, and the other a laparotomy five years ago. She did not know the character of the second operation.

Examination at the hospital showed a marked emaciation, her weight having dropped from her normal weight of 98 pounds to the present weight of 72 pounds. There were coarse tremors of the fingers, hands and arms. There was atrophy of the interossei muscles of both hands. A bilateral wrist-drop of mild degree developed in the hospital. There was gingivitis, dental caries and a grayish-blue line on the gums. The patient was restless and complained of severe headaches. The anemia was marked. Examination of the blood showed 45 per cent. hemoglobin, 3,600,000 erythrocytes, 9100 leukocytes and a moderate degree of basophilic granulation. The urine showed a trace of albumin and a few hyaline casts. The phenolsulphonephthalein test was normal. The anamnesis and the clinical and laboratory findings of the case suggested the diagnosis of lead poisoning very strongly. In carefully questioning the patient as to any possible source of exposure to lead the information was elicited that she had used "Flake White" face powder very freely for over fourteen years. As early as three years previously her dentists had remarked about a blue line on her gums.

This case shows that not only had the condition remained unrecognized for at least three years after unmistakable evidence of lead poisoning had developed, but that the symptoms at times had probably simulated surgical conditions and that the two previous operations very likely resulted from an improper diagnosis of the case. Mention of uncalled-for surgical intervention in cases of lead poisoning is not infrequent in the literature.

The most flagrant examples of the dangers lurking in lead-containing cosmetics and the facility with which proper diagnoses are overlooked will be found in the following four fatal cases of encephalopathia saturnina occurring in one family.

CASE II.—On August 30, 1920, a girl, L. F., aged sixteen years, Hospital No. 19,723, was brought to the University Hospital in an

ambulance in a stuporous, semiconscious condition. She was entered on the service of Drs. S. Marx White and R. I. Rizer, to whom we wish to express our gratitude for the opportunity of studying and reporting this case. The following history was obtained from the father of the girl:

The patient has always been strong and healthy. She has had the usual diseases of childhood: whooping-cough, diphtheria and measles. At the age of eight years she had acute nephritis. She had bronchitis and pneumonia twice before she was four years old, but without complications. She has had several mild attacks of sore-throat. Otherwise her past history has been entirely negative. Her present illness began about July 12, 1920, with an attack of sore-throat and severe headache, which lasted only for a day but left the patient in a very weak and easily fatigued condition. This weakness continued during the next two weeks. On August 1, 1920, she was suddenly seized with severe colicky cramps in the abdomen, which caused her to double up, vomit and cry out with pain. The attack lasted only for a few minutes and then passed away, but during the following week she experienced five similar attacks. The next week she was able to be up and around, but she complained of extreme nervousness and of pain in the legs and feet. She was taken to a hospital in a nearby town where she remained for a week, with no improvement. No diagnosis was made of her condition. She was then removed to a hospital in another town, where she remained for about a week. While in this hospital she sank into a stupor and became irrational and semiconscious, talking incoherently. The pain in the abdomen, arms and legs became very severe. She developed an obstinate constipation. There were twitchings of the muscles about the face and arms. She had several convulsions and became incontinent of her urine and feces. Her skin began showing an increasingly marked pallor. The physician who sent her to the University Hospital stated on her application that the diagnosis of this case had not been determined and that during the past year the patient's mother, sister and aunt had died under similar circumstances.

Physical examination on admission showed a fairly well-developed but poorly nourished young female with a mask-like expression of the face, lying quietly in bed in a stuporous and semiconscious condition. She was in no apparent pain or discomfort. Occasionally she would open her mouth as if she wanted to speak. She would respond sluggishly to commands, such as to protrude her tongue. The eyes were partially closed and showed no paralysis, ptosis or strabismus. Nystagmus could not be elicited. The left pupil was slightly larger than the right and somewhat irregular. Both reacted sluggishly to light. The lips were dry, cracked and encrusted. There was a very offensive odor to the breath. The tongue showed a coarse tremor. The gums appeared in good condi-

tion and showed nothing abnormal. There was a marked rigidity and stiffness of the neck. Attempted movements of the head seemed to cause pain. The heart and lung findings were negative. The abdomen was somewhat rigid and tender to deep palpation. It was otherwise negative. The extremities showed slightly hyperactive reflexes of the knees, ankles, biceps and triceps. There was no ankle-clonus, Babinski or Oppenheim present. Kernig's sign was positive. The blood-pressure was 118/75 mm. of mercury. A tentative diagnosis of tuberculous meningitis or lethargic encephalitis was made on admission.

Examination of the eye-grounds showed no choked disk, and because of the evidences of meningeal irritation a spinal puncture was performed. About 10 c.c. of clear limpid fluid were withdrawn. It escaped under slightly increased pressure. Examination of the fluid showed a cell count of 6 cc per millimeter. Nonne colloidal gold and Wassermann tests were negative. Examination of the urine showed a trace of albumin and an occasional granular and hyalin cast and a small number of leukocytes. Examination of the blood showed hemoglobin 45 per cent., erythrocytes 2,500,000, leukocytes 18,600. The differential count showed 88 per cent. polymorphonuclears, 7.5 per cent. lymphocytes, 0.5 per cent. eosinophiles and 4 per cent. basophiles. Several myelocytes were seen. There was a moderate anisocytosis and slight poikilocytosis. There was an occasional normoblast present, a moderate polychromatophilia and a very marked basophilic granulation of the erythrocytes. The basophilic granulation was the most striking finding obtained in the entire examination of the patient, both physical and laboratory. It was the more striking because it was so unsuspected. This finding at once suggested lead poisoning as a strong possibility in this case, but we were completely puzzled as to the source of exposure. We approached the father for further history. We inquired about the water supply and plumbing at their home. He said that they lived on a farm where they had an iron pump which had been there for many years, and that to his knowledge there were no lead pipes in the system. To all questions relative to the possibility of exposure to lead he was able to give no definite clue.

He volunteered, however, the suggestive information that this mysterious disease had peculiarly afflicted only the female members of his family, himself and ten-year-old son alone having been exempted.

Case III.—Concerning the histories and findings of the other members of the family, we were informed by the father and the doctors then in charge that L. P. F., an aunt of the patient, took sick about September 4, 1919, complaining of pains all over the body, great weakness and nervousness. She cried a great deal. The physical examination showed: "Well-nourished woman, rather

pale, with a pulse of 90 and a normal temperature. There was a systolic murmur at the apex but the heart was not enlarged. The knee-jerks were exaggerated. The blood examination was limited to the estimation of hemoglobin, which showed 70 per cent. A diagnosis of hysteria and a mitral lesion of the heart was made. In the latter part of November of the same year the patient was suddenly seized with violent convulsions; she died shortly afterward."

CASE IV.—V. F., a girl, about five years old, a sister to the patient, was first seen by the physician on March 22, 1920. She complained of severe colicky cramps in the abdomen with vomiting. The past history was unimportant. Physical examination showed a poorly nourished, very anemic child, having a waxen appearance. The heart was slightly enlarged and there was a loud systolic murmur at the apex. The spleen was palpable. The urine was not examined. Blood examination showed about 70 per cent. hemoglobin with 3,000,000 erythrocytes. On March 28 the physician was again called. He found the child in convulsions, from which she died several hours later.

CASE V.—Mrs. F., the mother of the patient, took sick with symptoms similar to those of the others. The attending physician gave no details other than stating that she died in convulsions from an unknown cause under circumstances similar to the other two deaths in the family.

This information furnished by the father and subsequently amplified by the attending physician led to a conviction that there was a common etiology for all four cases, and, as has already been mentioned, the case in the hospital suggested lead poisoning.

In subsequent inquiries the matter of face-powder was mentioned and the father then recalled that the aunt had introduced into his household in the latter part of the year 1919 a variety of face-powder known as "Flake White." This powder had been used by the female members of his family since that time. The aunt had used it for a number of months previous to this. She recommended it as being both good and inexpensive. The method of applying it was to make a thin paste by mixing it with water and rubbing it between the hands and then to work it well into the skin, giving special attention to the wrinkles. The result at first would be a grayish-white surface, which on drying became pearly white. The feature for which this powder especially recommended itself to the users was the lasting quality of each application. The father stated that he himself had always purchased it for them in bulk at the local drug store.

A quantity of this powder was purchased by him at our request and turned over to us for chemical analysis. The heaviness of the powder impressed us at once. We examined it chemically and found

this powder, known as "Flake White," to be pure lead carbonate. On inquiring we not only found that it was commonly sold by all drug stores, including the very best recognized ones, but that it was freely admitted by the druggists to be lead carbonate, ground into an impalpable powder. It was dispensed to the trade for cosmetic purposes and was used principally in the form of lotions. The father said that to his knowledge this powder was quite generally used in his neighborhood.

CASE II (continued).—The patient died on September 5, 1920, just seven days after her entrance into the University Hospital. During this short stay several of the symptoms characteristic of lead poisoning appeared. Throughout this period she had involuntary urination and defecation. Her condition on the different days of her residence in hospital was as follows:

First Day. Patient was comatose but appeared very sensitive to touch. She did not answer when spoken to. The temperature was 98.6°, pulse 120, respiration 18.

Second Day. Periodic twitchings of the muscles of the face and extremities developed. Patient had difficulty in swallowing. She appeared more stuporous. She was fed by nasal gavage. Temperature 101.2°, pulse 140, respiration 24.

Third Day. Patient appeared somewhat brighter during the morning. She attempted to speak several times but uttered no intelligible sounds. She appeared to be more conscious of her surroundings and protruded her tongue on command. Temperature 100.2°, pulse 140, respiration 22.

Fourth Day. No special change from the previous day.

Fifth Day. Patient again attempted to speak. There were marked twitchings and tremors of the muscles of the face and hands. It was decided to start the administration of small doses of potassium iodide. She received two doses of three minims each of the saturated solution.

Sixth Day. Patient appeared more conscious and alert, but very irritable. With a little assistance she sat up in bed and drank a glass of eggnog, the first food she had swallowed by herself since her entrance. Both wrists showed marked weakness, which later in the day developed into mild wrist-drop. A faint bluish line appeared on the gum of the lower jaw. She received three doses of three minims each of potassium iodide solution. Temperature 102°, pulse 145, respiration 30.

Seventh Day. The bilateral wrist-drop became very pronounced and the blue line on the gums became plainly visible. The respirations were more rapid and the general condition of the patient was definitely less favorable. The potassium iodide solution was discontinued and stimulants were administered. In the morning the temperature rose to 103° and in the afternoon it reached 105°.

The pulse averaged about 150 and the respiration about 30. Crepitant and subcrepitant rales were elicited over both lungs posteriorly, but no evidences of consolidation were present. There developed a marked cyanosis. The pupils became unequal and extremely rapid spasmodic changes in the size of the pupils occurred. They contracted and dilated very suddenly, these variations not being due to any change in the intensity of the light in the room. She sank very rapidly and died on this day at 4.25 P.M.

Laboratory Examinations. Several examinations of the urine showed a faint trace of albumin with occasional granular casts and leukocytes. Because of the incontinence it was impossible to collect large quantities of urine for purposes of chemical analysis; however, about 300 c.c. were collected up to September 2. This was evaporated and tested for lead but the reaction proved negative. There is a possibility that if the urine voided after the administration of the potassium iodide had been tested for lead a positive reaction might have been obtained. Negative tests for lead in urine are not uncommonly encountered in cases of chronic lead poisoning.

Repeated examinations of blood smears stained with Wright's stain showed an average of 83 per cent. polymorphonuclears, 7 per cent. lymphocytes, 4 per cent. large mononuclears, 2 per cent. transitionals, 2 per cent. basophiles and 2 per cent. neutrophilic myelocytes. As previously mentioned the striking picture in the blood smears was the very marked basophilic granulation of the erythrocytes. Fig. 1 shows a drawing of an actual field of a smear as seen under the microscope with the oil-immersion lens. Fig. 2 shows a composite picture of various types of basophilic granulation and polychromatophilia encountered. The number of red blood cells involved varied with the quality of the staining as well as of the stain, which would indicate that the failure to find basophilic granulations in cases of lead poisoning is often due to faulty technic. Schnitter[9] calls attention to this fact when he states that in his early investigations of lead poisoning he rarely encountered basophilic granulations in the blood cells, but after he perfected his staining technic he was able to demonstrate the granulations in almost 100 per cent. of his cases. Well-stained smears in our case showed 3.2 per cent. of erythrocytes to be affected by the basophilic granulation, which represents the enormous figure of 32,000 in every million cells. When one considers Trautmann's[10] dictum that more than 100 affected cells per million generally means lead poisoning and that more than 300 affected cells per million is sufficient evidence of lead poisoning for forensic medicine, one can appreciate the significance of the above figures.

Besides the basophilic granulation there was also considerable diffuse polychromatophilia. This diffuse basophilia involved about an equal number of cells as the granular basophilia. The granules in the cells varied in size, shape and the number present in each

cell. Some of the granules are rather coarse, and, as a rule, are relatively few in number. Others are very fine and fairly numerous.

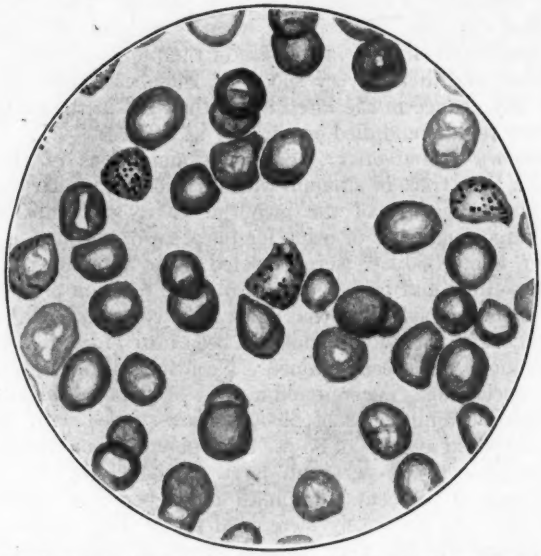

FIG. 1.*—Drawing of an actual microscopic field of a blood smear stained with Wright's stain stain, from Case II. (No. 10 ocular, oil-immersion objective.) Note the relatively large number of granular cells and the coarseness of the granules.

They are basic staining, round or angular, and occasionally appear like small rods resembling bacilli. The majority of the granules

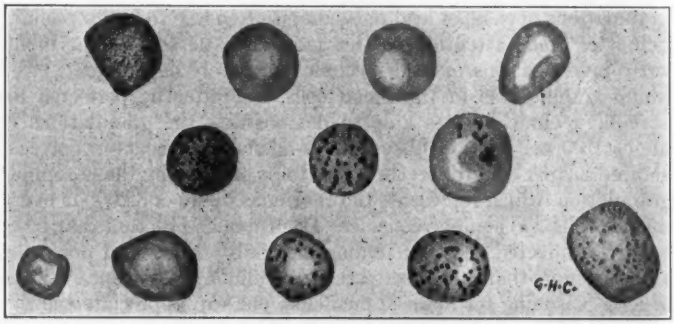

FIG. 2.*—A composite picture (drawing) of pathological cells encountered in the blood smears. Note the variations in size, shape and number of these granules.

* Figs. 1 and 2 are from drawings in color made by Mr. G. H. Childs, of the art department in the Department of Anatomy. All photomicrographs were made by Mr. Henry W. Morris, of the Department of Pathology.

are the shape of cocci, though somewhat smaller, and are often grouped in pairs like diplococci. The other changes in the red blood cells are not very marked. There is a moderate degree of anisocytosis and a slight degree of poikilocytosis present. There is no doubt but that the blood picture in this case is absolutely pathognomonic of lead poisoning. The surprising feature to us is that in spite of so definite and characteristic a blood picture the case had not been correctly diagnosed before entering the University Hospital.

Autopsy Protocol. An autopsy was performed on this case sixteen hours post mortem. As was to be expected in a case of lead poisoning there were few gross lesions present. The principal findings are as follows:

The body is that of a fairly well-developed but poorly nourished female, aged sixteen years. There is no edema and no jaundice. There is marked pallor and blanching of the skin and mucous membranes. There is a faint bluish line along the margin of the gum of the lower jaw. The heart has a yellowish-brown color and is flabby. The dependent portions of the lungs are slightly heavier than normal; droplets of mucopus can be expressed from the bronchioles. There are no areas of consolidation. The spleen is about twice the normal size; the pulp is soft. Liver and gastro-intestinal tract show no gross lesions. The left kidney weighs 75 grams, the right 100 grams. There is marked postmortem autolysis present. There are multiple nodules (abscesses), 1 to 3 mm. in diameter, scattered through the parenchyma of the right kidney. The intervening tissue between the nodules appears normal. The left kidney shows no gross lesions. In removing the brain a fairly large quantity of cerebrospinal fluid escapes. Examination of the brain reveals no gross lesion. The entire brain is preserved for histological study.

Lead was found in the liver and the left kidney by chemical analysis. For this we are indebted to Mr. J. P. Quigley, of the Department of Pharmacology. This final analysis established incontestably the diagnosis of lead poisoning in this case.

Microscopic examination of most of the tissues and organs revealed very little of interest and will therefore be omitted here. Only the tissues showing pathological changes will be considered.

A section of the heart stained with Sudan III shows a slight increase of interfibrillar fat within the muscle fibers. The lungs show slight congestion and a few minute patches of bronchopneumonia. The liver shows a moderate degree of fatty metamorphosis around the central veins and a slight round-cell infiltration into the periportal spaces. Sections of the right kidney show miliary abscesses in the cortex and a few also in the pyramids. There is extreme postmortem autolysis present throughout, and this greatly hampers a careful histological study. Sections from both kidneys stained with Sudan III reveal the presence of large

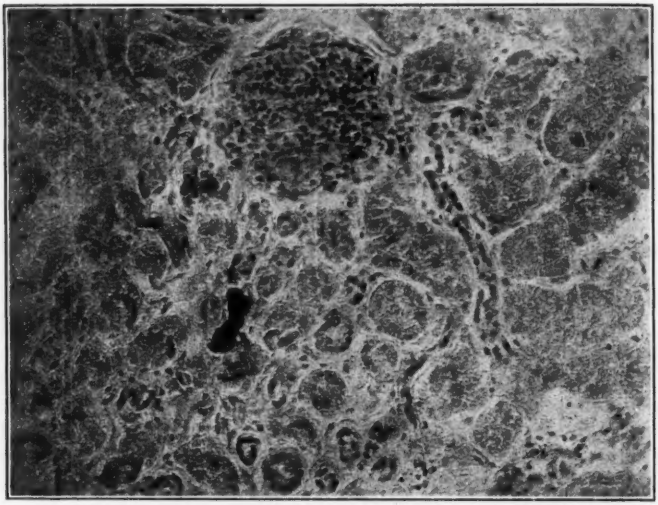

FIG. 3.—Photomicrograph of section of kidney. The postmortem autolysis is marked; this explains the peculiar appearance of the glomerulus. Closely packed rosette-shaped masses of lime salts are seen deposited in a degenerated tubule from Henle's loop.

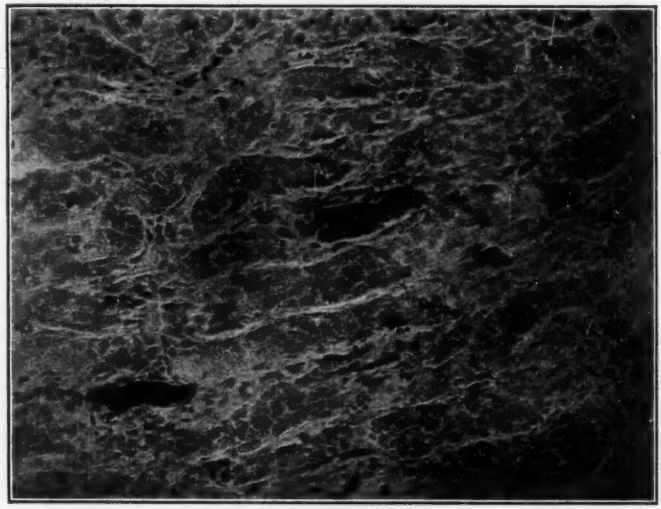

FIG. 4.—Photomicrograph of section of kidney showing several degenerated convoluted tubules filled with masses of lime salts.

and small fat droplets within the epithelial cells of segments of convoluted tubules. There are occasional large clumps of lime salts, some shaped like rosettes, filling up many degenerated collecting tubules and loops of Henle (Figs. 3 and 4). The amount of lime salt deposit is quite striking, and the changes in the kidney other than the accidental abscesses resemble very strongly the lesions produced by mercurial poisoning. The glomeruli show no definite lesion.

We are indebted to Dr. J. C. McKinley, of the Department of Neurology, for furnishing us with excellent sections from all of the different areas in the brain as well as for his assistance in the study

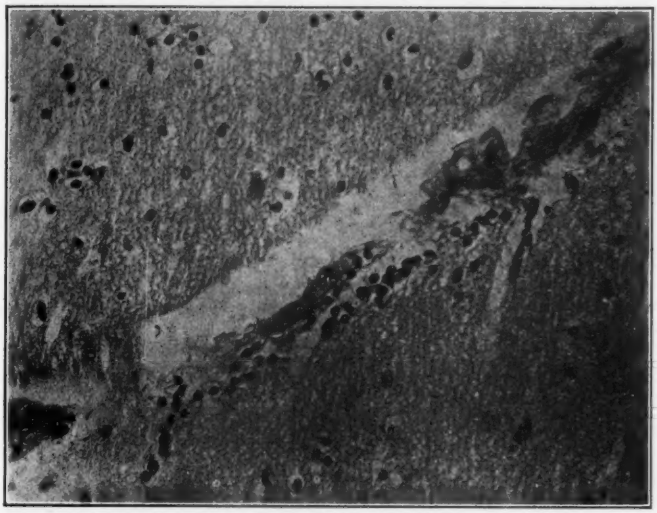

FIG. 5.—Photomicrograph of section from the midbrain. Note the narrow arteriole surrounded by several rows of lymphocytes, more marked on one side. Most of the sections show a clear space between the vessel wall and the surrounding tissues. This may be an artefact due to shrinking.

of these slides. Considering the intensity of the clinical symptoms the pathological lesions found in this brain are surprisingly meager compared with those of lethargic encephalitis, where the histological changes are often very profound, even in cases presenting mild clinical cerebral manifestations. The more intense lesions—and these are relatively insignificant—are in the sections from the thalamus, the lenticular nucleus and the midbrain. Here and there are seen slight perivascular round-cell infiltrations around the small arterioles. Sections from the midbrain (Fig. 5) and from the lenticular nucleus (Figs. 6 and 7) show the perivascular infiltration very plainly. In the lymph spaces surrounding many of these arterioles

are seen clumps of large phagocytic cells containing granules of bluish-green crystalline-appearing pigment. We do not know the

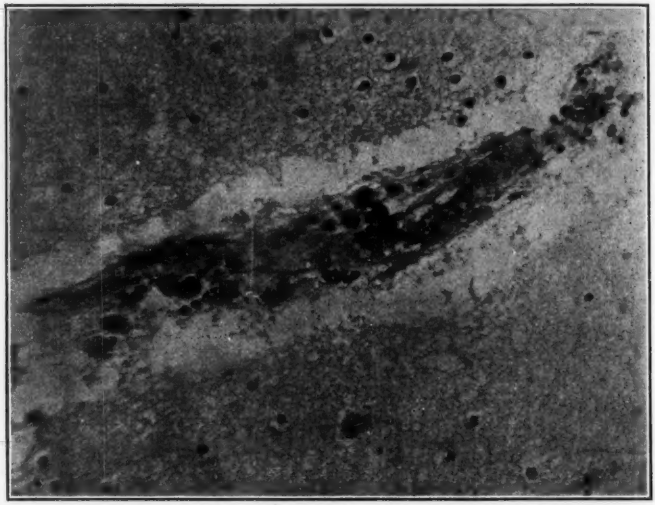

FIG. 6.—Photomicrograph of a vessel in a section from the lenticular nucleus. Note the large phagocytic cells containing a greenish crystalline pigment surrounding the vessel.

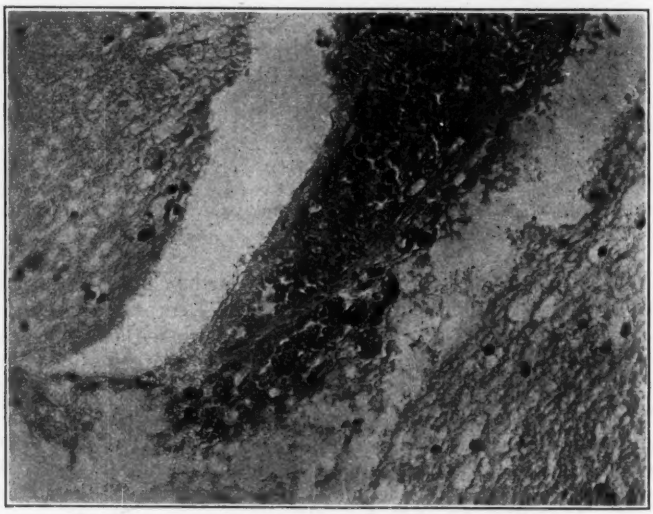

FIG. 7.—Photomicrograph of a larger vessel than in Fig. 6. The perivascular infiltration of large phagocytic cells containing the pigment granules is well shown.

character or the significance of these pigment granules. No microchemical tests were used for their identification. This pigment does not resemble the ordinary blood pigments, hemosiderin or hematoidin, nor is it opaque enough to represent particles of lead or its compounds. It may consist of phagocytized material of the basophilic granulation; if so it is fairly characteristic of the disease. Monakow[11] mentions a similar pigment. In the routine histological studies of brains in various other diseases we have not encountered this type of pigment. In the intima of some of the small arterioles there appears to be a proliferation of the endothelial cells.

Changes are also present, though slight, in the ganglionic cells themselves. Neuronophagia and satellitosis are occasionally encoun-

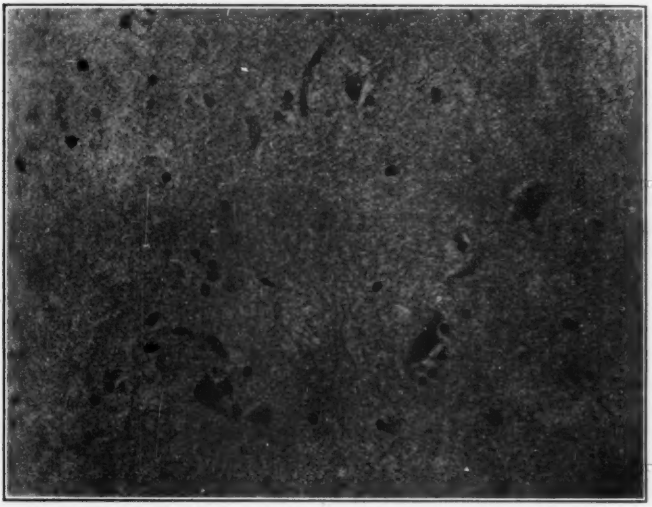

FIG. 8.—Photomicrograph of a section from the thalamus. Note the neuronophagia and satellitosis.

tered in some of the slides, but are most evident in sections from the thalamus (Fig. 8). It is difficult to determine whether the degenerations of the cells are due to the direct toxic action of the lead or are secondary to the changes in the bloodvessels. One of the bloodvessels in the thalamus (Fig. 9) shows complete occlusion by a mass of round cells, principally lymphocytes. The vessel is very thin-walled and there is considerable edema in the tissue immediately surrounding it. We do not know whether there is any significance in this type of lesion.

Discussion. The clinical evidence, the laboratory evidence and the evidence obtained at postmortem, supported by chemical analysis of the organs, prove this case, beyond peradventure of a

doubt, to be one of lead poisoning, and that poisoning to be due to the use of a lead-containing cosmetic. It appears to be evident that the three other members of the family had been stricken during the course of the year by the same cause.

The aunt (Case III) had presented symptoms of weakness, nervousness and pains all over the body, anemia and frequent crying spells. The diagnosis in this case was hysteria. These symptoms are very common in lead poisoning. In fact, Charcot has given many characteristic examples of cases which he termed "hysterie saturnine." Oliver[15] states that some cases of encephalopathia saturnina begin like hysterical attacks with crying and laughing and death often follows within a few days of the onset.

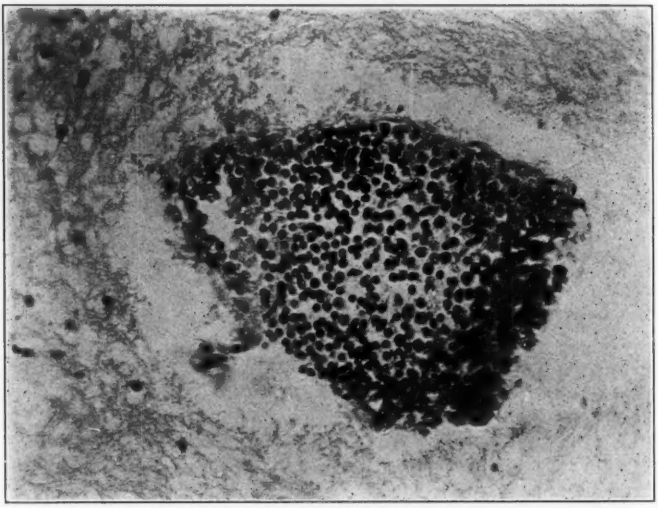

FIG. 9.—Photomicrograph of section from thalamus showing a cross-section of a fairly large thin-walled vessel completely filled with lymphocytes, a few endothelial cells and a few polymorphonuclears.

Case IV, that of the five-year-old girl, had also presented symptoms of lead poisoning, such as severe colicky cramps, vomiting and anemia. Death occurred in convulsions. This fact, together with the symptoms and the course of the disease, points very strongly to that conclusion, especially when considered in conjunction with the other cases. It is easy to assume that the exposure to the lead in this case probably occurred through the handling of the child by the other female members of the family at times when their hands were contaminated with powder, and we might also assume that, like other children, she had at different times dabbled

her face and hands with the powder of the women of the household. It is a well known fact that poisoning from lead does not depend upon the quantity ingested, inhaled or absorbed but upon the constant repetition of doses over a long period of time, however minute those doses may be.

The mother (Case V) died in convulsions. Although her symptoms are not given in detail either by the father or the attending physician, both stated that the circumstances of her sickness and death were entirely similar to those of the other affected members of the family.

We have thus far presented definite evidence of one case of non-fatal lead poisoning (Case I), one case of fatal lead poisoning (Case II), and three other cases of fatal poisoning in the same family as Case II, in which the presumptive evidence is so strong as to justify the conclusion that all five cases of poisoning were due to the use of a lead-containing cosmetic, dispensed in most if not all of the drug stores under the trade name of "Flake White." Besides these cases we have record in the literature of two similar cases in which the victims are reported to have used the very same powder. It was by mere chance that the true nature of these five cases was finally discovered. It requires therefore no great stretch of the imagination to realize, what cannot be too often repeated, that with the widespread dispensing of this powder for cosmetic purposes—without limitation—the number of persons suffering from the effects of this cosmetic whose condition remains unrecognized must be legion. The practice of using "Flake White" as a cosmetic is therefore definitely a menace to public health and demands attention of the health authorities.

Industrial and Miscellaneous Forms of Lead Poisoning. In connection with the study of these cases of poisoning from cosmetics it may be of interest to discuss lead poisoning in general, with special reference to the pathology associated with the various characteristic symptoms.

As has already been stated, lead is the commonest of all industrial poisons. Lead poisoning is encountered among painters, lead-smelters, paint manufacturers, plumbers, file-makers, linotypers, putty-makers and among workers of many other industries too numerous to mention. According to Oliver the causes of lead poisoning in painting, one of the occupations most commonly affected, are as follows:

1. Mixing of paint (dust).
2. Holding brush between the teeth.
3. Not washing the hands before eating.
4. Sandpapering of painted surfaces, which produces dust that is inhaled.
5. Burning off old paint, which produces fumes that are inhaled.

Accidental poisoning may come through drinking water which has passed through lead pipes or has been stored in lead-lined cisterns (Osler,[5] Oppenheim.[3]) Rosenau[1] states that this form of poisoning is more common than it is given credit for.

Lead poisoning may also occur from the solder in canned goods, from utensils lined with lead, various beverages, false teeth and thread and snuff containing lead. It has followed the use of lead and opium pills, lead ointment and in infants from the application of lead wash to the mothers' nipples. Osler reports an outbreak of lead poisoning in Philadelphia from the use of baking-powder containing lead chromate.

At this point it may be of interest to quote two cases cited in the literature of poisoning from unusual sources:

One case is reported by Stefanowicz[12] of a woman, aged thirty years, who developed lead poisoning from an apparently unexplainable source. She presented the characteristic blue line on the gums, bilateral radial palsies and complained of colic. Stefanowicz went out to her home in the country in order to investigate any possible sources of exposure. He observed a pile of kindling wood which had paint on one side lying near the house. This wood had come from an old painted building which had been torn down. Upon investigation it revealed that the woman baked her bread in a large open oven heated with this kindling wood and that the ashes were allowed to remain on the stones. The fact that a toothless old grandmother who could use only the soft part of the bread and a young child who preferred that part were both exempt from this poisoning, while the patient, who alone ate the crust, was affected, led to the conclusion that the bottoms of the loaves of bread became impregnated with the lead from the paint which had settled down as a fine heavy dust on the surface of the stones. Chemical analysis of this dust corroborated the presumption.

Rand[13] cites a case of the development of symptoms of lead poisoning in a dairyman who drove a milk wagon into town every morning. The water supply was neither pumped nor piped and therefore could not be considered a source of the poisoning. It was learned that the man had been drinking beer from bottles which had been cleansed with lead shot, and examination revealed the presence of some of the lead shot in the bottles which had not been removed after the cleaning.

Statistics. The number of deaths from lead poisoning is truly appalling. Hamilton[14] reports that in a period of sixteen months, from January, 1910, to April 3, 1911, there were 358 cases of lead poisoning with 23 deaths in twenty-three white-lead factories in the United States. Oliver[15] states that in ten years in England there were 1973 cases of poisoning reported in house painters and plumbers alone with 393 deaths. In Paris out of 300 patients admitted into the hospitals for lead poisoning 233 were house

painters. Osler reported 60 deaths in England and Wales during 1916. In the United States he reports 147 deaths in the registration areas during 1917.

All investigators mention the fact that females are more liable to plumbism than males. The proportion is given as four to one.[5] There is a special tendency among women to the cerebral encephalopathic forms. It is almost impossible for a pregnant woman working in a lead industry to give birth to a healthy child.[1 15] There occurs either abortion, miscarriage or the early death of the child from convulsions. Curiously enough this often happens in a high percentage of cases when only the father works in lead industries. This has also been found to be the case experimentally in animals.[16] Sterilization of the male is also not uncommon. That lead passes from the mother to the fetus is evident from the fact that it has been found chemically in the organs of the infants of lead-workers.

Women who take lead pills for producing abortion often die of the effects. The abortion is brought about by the killing of the fetus and by the stimulation of the uterine muscles to contraction.

Period of Exposure. There is no specified length of time for the development of lead poisoning. It is given as all the way from a week to ten years. The largest number of cases occurs during the first few months of exposure. Cases are reported in which the exposure was less than two weeks. Oliver reports a case of a woman dying of encephalopathia saturnina in three months. The length of time of exposure in the four fatal cases here discussed cannot be definitely given but can be safely stated to have been under one year.

Routes of Absorption. Lead gains entrance into the body by three routes: (1) Swallowing of minute particles of the substance; (2) by inhalation of lead dust or the fumes of lead in a molten state or the vapor of lead in a fused state, and (3) by absorption through the skin. It is the consensus of opinion of most investigators that the gastro-intestinal is the most common and the skin the relatively unimportant route. In the respiratory route the moisture, heat and carbon dioxide from the lungs help transform the insoluble carbonate into the soluble bicarbonate. In the gastro-intestinal route the saliva is supposed to have a slight solvent action on the carbonate in the mouth while the hydrochloric acid of the gastric juice changes the carbonate into soluble chlorides. The soluble lead compounds then combine with the proteins, forming an albuminate of lead. It has been found that the lead is more readily absorbed through an empty stomach, especially when there is hyperacidity or hypersecretion present. Absorption through the skin is facilitated by the fatty acids of the perspiration, which also help to transform the insoluble into soluble compounds. Oliver mentions the occurrence of cases of lead poisoning through the absorption of lead through the skin of the hands from the washing of painters'

overalls. In our series of cases as well as in the cases cited by Holland the entrance of the lead face powder into the system might have occurred through all three routes. However, it is very likely that in these cases absorption through the skin played an important part, since the perspiration which so frequently covers the face would assist this process of absorption.

Patterson[2] claims that the *inhalation* of dust or fumes is the chief source of industrial poisoning and that this method is more dangerous and produces symptoms earlier than the *ingestion* of larger quantities of the same compound.

Rand[13] mentions the discovery of lead in the blood plasma and believes this to be of the highest importance for purposes of diagnosis. This finding explains the manner in which lead is distributed through the body. It is thought that it exists in the plasma in the form of an albuminate.

From the plasma the lead is absorbed by the various organs and tissues of the body, chief among which is the liver. In the organs it may be stored for very long periods of time. Cases are reported in which lead has been eliminated from the body eighteen years after the patient has ceased working in lead industries. Grawitz[17] states that lead which is stored in the body may be liberated months afterward, causing symptoms such as optic atrophy, encephalopathia, etc. It has been found chemically in practically all of the organs and tissues of the body; glandular tissue (liver) and nerve tissue (brain) especially store large quantities of it.

Routes of Elimination. Lead is excreted through the kidneys, intestines, stomach and probably the sweat. During the acute stages of lead poisoning lead is frequently found in appreciable quantities excreted in the urine. This fact is often made use of in the diagnosis of this form of poisoning. Lewandowsky[4] states that the excretion takes place also through the milk and saliva. He states that the kidneys excrete it in quantities only when the body is saturated. In the later stages excretion is principally through the intestines, especially by means of migrating leukocytes. Because of this excretion through the digestive tract in severe cases hemorrhages and superficial ulceration may occur in the mucosa. That the stomach is also an important avenue for the excretion of lead is demonstrated by the fact that lead has been found in the vomitus (as well as in the urine and feces) as late as sixteen months after the subject has ceased to be exposed to lead. Unfortunately in our cases we did not test the feces for lead.

Susceptibility. Not all individuals are equally susceptible to the toxic effect of this metal. The sex predisposition has already been alluded to. There also appears to be a familial predisposition. Members of some families working under the same conditions as the individuals of other families who have been severely affected may show no evidence of ill-effects.

Patterson lists the conditions predisposing to lead poisoning, as alcoholism, defective teeth, gastro-intestinal disorders, constipation. Schnitter adds to the above diabetes and epilepsy. The number of hours of labor seems to be an important factor. In some factories in which there had been no record of poisoning there developed several cases following a change from six hours to eight hours per day.[15] Persons who have been previously affected appear to have an increased susceptibility. As has already been mentioned, individuals with gastric hyperacidity are especially prone to the effects of lead. Since it is known that an empty stomach exposes the laborer to intoxication, many establishments urge their employees to eat a heavy breakfast before coming to work.

The principal compounds of lead which produce poisoning are oxide, acetate and carbonate. It is the last which we found to be on the market under the trade name of "Flake White." For a time it was thought that the sulphate because of its greater stability should be substituted for the carbonate in the lead industries and thus decrease the possibility of poisoning; but on experimentation it was found that the sulphate was just as readily transformed into the soluble salt.[2]

Animal Experiments. Erlenmeyer[18] performed a number of experiments on cats to determine the relation of the quantity of lead to the degree of poisoning. He injected the cats subcutaneously with lead carbonate. They died with symptoms of cramps, colic and bulbar palsies in from forty-seven to one hundred and twelve days. The majority died within about sixty days. For the production of chronic poisoning he found that the question of time was more important than quantity, a finding well borne out clinically. He found that about 1 mg. of the lead salt per kilo per day over a period of about fifty to sixty days was sufficient to produce chronic poisoning. He concluded from his experiments that it is necessary to have a certain saturation of the body continued over a rather prolonged period of time in order to produce poisoning. This strongly suggests the possibility of the repeated entrance of the lead into the body in amounts so subminimal as to produce toxic effects unrecognizable as lead poisoning. Nevertheless the body undoubtedly suffers from the deleterious effects of even these small quantities. It is reasonable to assume that lead-containing face powder, because of the very nature of its application, may bring about just such results, multiple indeterminate symptoms of which the etiology remains unknown. Such cases would receive only symptomatic treatment; the true causative factor would remain untreated.

Symptoms. The symptoms of lead poisoning are variable. Among the earliest signs, according to Oliver, are pallor, loss of appetite and tendency to vomit. There may be associated sallowness and cachexia. The patient feels tired and often develops an obstinate constipation and the tongue becomes coated. In severe

forms there may develop convulsions without any previous complaints. The emaciation and cachexia may appear very rapidly. According to Apfelbach[19] the symptom complex depends upon certain factors: (1) Dosage and rapidity of the dosage; (2) presence of alloys in the metals ingested; (3) method of entrance, whether through inhalation of fumes or through inhalation or swallowing of lead dust; (4) individual susceptibility, such as sex, age, habits, etc. The most common symptoms in the order of their importance are: (1) Colic, (2) constipation, (3) pallor and anemia, (4) blue line on the gums, (5) basophilic granulation, (6) tremor, (7) palsies. The nervous symptoms sometimes predominate even in the acute forms,[4] but are by far more common in the chronic. Headaches, dizziness, ataxias, paralyses and disturbances of consciousness, such as coma, delirium and confused excitement and stupor, often occur in this type of cases. The effect upon the nervous system is generally primary and only in a small percentage of cases is it secondary to disease of other organs. Lewandowsky emphasizes the slowing of the pulse during the attack. The pulse is full and of high tension.

Colic. The most common symptom—colic—is often the first to appear. It generally manifests itself by a sudden development of cramp-like, sharp, cutting pains which may be agonizing in character at or above the umbilicus. Often the pains radiate into the hypogastric and hypochondriac regions. Sometimes the pain simulates appendicitis, and when this is associated with vomiting and constipation it may be mistaken for intestinal obstruction. Frequently the pain is relieved by pressure, and this is considered by some to be especially characteristic of this type of colic. The attacks rarely last more than fifteen minutes. Prodromes of nausea, bad taste in the mouth, constipation and abdominal distress are not uncommon. Even between the attacks the patient is not entirely free from some distress. In contrast to hepatic or renal colic there is rarely any perspiration associated with even the severest of these attacks. The temperature is usually subnormal.

There are a number of theories advanced relative to the causation of colic. Frank[20] explains colic by the increased tonus or spasm of the splanchnic vessels brought about by the action of the lead. Oliver states that the colic is the result of strong tonic contractions of segments of the intestine. The violent contraction of the muscle fibers also forces the blood out of the splanchnics, raising the blood-pressure, hardening the pulse and at the same time slowing the pulse-rate. The cause of the spasm, he believes, is due to the stimulation of the peripheral nerve-endings, as evidenced by the fact that nitrates and atropin usually relieve the attack. Some investigators claim that the colic is due to the direct action of the metal on the muscle fibers of the intestine, while others state that it is due to a stimulation of the vasoconstrictors. Lewandowsky believes that the colic is the result of several factors acting simultaneously

upon the intestines. The symptoms are probably due to a stimulation of the motor nerve elements together with a direct stimulation of the smooth muscle fibers both in the wall of the intestine and of the bloodvessels. That lead acts toxically both on nerve elements and on non-striated muscle fibers is quite generally conceded and the production of abortions as well as palsies well illustrates that fact. Kussmaul and Maier[21] found sclerosis of the celiac axis in some cases. This is not a constant finding and is probably a secondary process.

Anemia. The pallor in cases of lead poisoning may be due to causes other than the degree of anemia present. According to Naegeli[22] the paleness of lead-workers is commonly due not to the anemia but to the contraction of the superficial bloodvessels. Only in the chronic cases of poisoning does a true anemia develop.

Grawitz[17] denies this. He and von Behrend showed in 1899 that lead was a peculiar blood poison which acted directly upon the red blood cells, affecting chemically the hemoglobin without producing hemolysis. The average blood picture in lead poisoning is about 50 per cent. hemoglobin, 2,500,000 erythrocytes and 12,000 leukocytes. There is generally moderate anisocytosis, mild poikilocytosis, moderate polychromatophilia and an occasional nucleated red blood cell. The striking feature in the blood picture is the presence of basophilic granules within many of the red blood cells. There is a great diversity of opinion as to the importance of this finding. Naegeli and his followers deny that this is very characteristic. Trautmann[10] believes it to be of great importance. He found that in less than 2 per cent. of cases other than lead poisoning there are involved more than 100 cells per million while in lead poisoning the figures may reach more than 100,000 per million. Schnitter[9] in his early studies of blood changes in lead poisoning found very many cases without any basophilic granulation. In his later studies, however, after he improved his staining technic with methylene blue stains, he found granules present in every case in a series of 88 cases. He could substantiate his presumptive diagnosis by a single examination of a blood smear. He supports Grawitz as to the extreme importance of this finding in cases of lead poisoning. From a prophylactic standpoint the examination of the blood of lead-workers for these granules is important, since not infrequently they will be present in the red blood cells before symptoms occur. The number of cells affected is generally proportional to the severity of the disease.

Basophilic granulation is found in conditions other than lead poisoning. They have been found occasionally in malaria, pernicious anemia, pseudoleukemia, chlorosis, posthemorrhagic anemia and tuberculosis, but practically never in excess of 300 per million cells.[10] Schnitter encountered less than 500 affected cells per million in only 5 per cent. of his series of 88 cases of lead poisoning. In 26 per cent. there were from 1000 to 5000; in 3 per cent. from 40,000

to 50,000; and in one case more than 100,000 per million. In our case (Case II) we found 32,000 per million. We must agree with Grawitz on the importance of basophilic granulation, for in two of our cases (Cases I and II) the diagnosis was made on this finding alone.

The origin of these granules is still a matter of controversy. Ehrlich, Askanazy, Schaumann, Naegeli and others considered the granules as nuclear remnants arising as an end-process from karyolysis. Grawitz takes exception to this, stating that the granules are degenerating products as the result of a toxic effect upon the cytoplasm. This concept explains the term "granular degeneration," which is so commonly applied to these granules even in many text-books. He states that basophilic granulation is not found in normal blood either in the fetus, newborn or adult, nor is it to be found in the bone-marrow. He believes that the granules arise within the red blood cells of the circulating blood through the degenerative toxic action of various poisons upon the protoplasm. The most important of such poisons is lead. He bases his theory on the following reasons: (*a*) Granular degeneration is not found in the bone-marrow even in cases in which great numbers of affected cells are present in the circulating blood; (*b*) it is scarcely if ever found in normal blood; (*c*) the granules are usually fine and numerous while remnants of nuclei are usually coarse and few in number; (*d*) they are tinctorially different from nuclear remnants; (*e* they are found in erythroblasts with perfectly round intact nuclei; (*f*) they are not found in regeneration of blood following hemorrhage; (*g*) they are present in cases of lead poisoning in which no nucleated reds are present; (*h*) they are not demonstrable with ultraviolet light which shows the absence of nuclear material.

Askanazy and Pappenheim believe that the granules arise from the toxic effect of the lead-containing serum on the basophilic substance of unripe chromatophilic cells. This Grawitz holds as untenable, since often there are cases with extensive granular degeneration which present practically no polychromatophilia.

Naegeli disagrees with Grawitz on many points. He denies the frequency of this degeneration in lead poisoning, asserting that it is constant only in very severe anemias. He failed to find it even in cases in which there was a lead line present on the gums and when lead was found in the urine. He states that it runs parallel with polychromasia. He agrees with Ferrata that the origin of these granules is from nuclear remnants and therefore they are signs of regeneration. He gives as his reasons the following: (*a*) They are frequently present in the embryonic blood of animals; (*b*) they are absent in aplastic anemias; (*c*) they have been found in certain stages of human embryos; (*d*) they have been found in experimental anemias produced by hemorrhages.

Ferrata[23] has changed from his former view that the granules

are derived from parachromatin of the nucleus. He now agrees with Pappenheim and Askanazy that they are of cytoplasmic origin. He believes that the erythrocytes, which normally even in adults, pass through a polychromatophilic phase in order to reach the final acidophilic state, undergo "conglobation" of the basophilic substance under various pathological states and thus form the basophilic granules. These later studies tend to show that neither Grawitz nor Naegeli was technically correct and that basophilic granulation is evidence not of degeneration but of regeneration; this regeneration, however, is pathological.

Lead Line. The blue lead line on the gums is another important sign, though its absence does not preclude the diagnosis of lead poisoning. As already mentioned the lead which has been absorbed is carried in the blood stream as the soluble albuminate. Traces of this are often deposited as a grayish-black sulphide in the superficial layers of the mucous membrane of the gingiva by the action of hydrogen sulphide present in the tartar of the teeth. The line may form within a few days after exposure and may remain for weeks or months. The precipitate is located principally at the apices of the papillæ within endothelial cells of the capillaries and neighboring tissues. The deposit is most marked around the incisors and especially next to carious or ill-kept teeth. Patches are often deposited in the cheek where the mucous membrane lies in contact with decayed teeth and infrequently also in the lips.[24] Pyorrhea sometimes develops simultaneously with the lead line.

Tremor. Lewandowsky and Apfelbach speak of the early occurrence of a tremor of the tongue, fingers and hands. This tremor of the muscles may be fine, resembling that of hyperthyroidism or coarse like that in paralysis agitans. In Case II the tremor was rather fine and very pronounced in the latter part of the illness.

Palsy. Degenerative changes in the peripheral nerves are quite constant, producing the so-called "lead palsy." This affects principally the extensors of the hands and fingers and is usually bilateral.[24] The localization seems to be determined by the activity of the muscles. Some authors claim that the degeneration is in the anterior horns of the cord.[4] The little change found in the cord post mortem is explained by the supposition that the change in the ganglionic cells is only functional. However, the peripheral nerves show definite lesions. There is often an absence of the axis-cylinder and an increase in the connective tissue. Occasionally there is a multiplication of the nuclei of the sheath of Schwann. Seifert[25] states that the lead paralysis is the result of a combined degenerative peripheral neuritis and myositis. There are degeneration, atrophy and fatty changes in the contractile substance of the muscle fibers followed by fibrosis.

Arteriosclerosis. Lead workers are notoriously susceptible to arteriosclerosis, which in turn often results in contracted kidneys

and hypertrophied heart. Disturbances of vision and blindness may be due to hyaline degeneration of the arterioles and capillaries of the optic nerve, retina and choroid.[26] Seifert found atheromatous patches in the basilary artery. Kussmaul and Maier describe chronic inflammatory changes in the arterioles resulting in decreased elasticity of the vessels, which they believe is responsible for the cerebral apoplexies and encephalomalacias occasionally encountered in lead poisoning. According to these authors the lesion is chiefly a hyperplasia of the media.

Nephritis. The kidneys often suffer very severely in chronic plumbism. Kauffman places lead poisoning as foremost among the intoxications, producing chronic induration or the so-called chronic interstitial nephritis. From what has already been said about the toxic effect of lead on arterioles it is strongly suggestive that the lesion in the kidney is not really a true nephritis, but more probably an arteriosclerotic change. Those who study the histopathology of kidney lesions know that there is still great confusion in the identification of kidney conditions, and what is often diagnosed as chronic interstitial nephritis is in reality an arteriosclerotic kidney. Kauffman in discussing this type of lesion states that there is a gradual fibrosis of the glomeruli with atrophy of the associated tubules and a proliferation of the connective tissue together with a round-cell infiltration. Some glomeruli remain normal or are even hypertrophied. In Case II of our series the kidney changes were more degenerative than inflammatory and can best be classified under the toxic nephroses.

Arthralgias. A symptom often associated with lead colic, but quite distinct from it, is arthralgia. This consists of sharp, shooting pains in the flexor muscles of the lower or upper extremities which may extend into the joints and bones. Often the joints become swollen.

Encephalopathia Saturnina. One of the most interesting as well as the most serious manifestations of lead poisoning is the symptom-complex designated as encephalopathia saturnina, exhaustively described by Tanqueral des Planches[27] in 1836. Cases III, IV and V as well as Case II belong to this group of saturnism. The cerebral symptoms are numerous. The eyes may show ocular palsies, hemianopsia and amaurosis. Neuroretinitis and papilledema are frequent. The blindness is sometimes preceded by headache and convulsions. Retinal hemorrhages occur. Some of the general symptoms are apoplexy, delirium, convulsions, epilepsy and coma. Death often occurs in convulsions or coma.[3]

Of the psychoses, epilepsy is important. Acute psychoses which develop in the course of a month are relatively rare. In these cases there is a severe dulling of consciousness with motor changes. The symptoms sometimes set in suddenly but usually are preceded by prodromes of headache, dizziness, insomnia, hallucinations,

restlessness and fits of melancholy. The chronic psychoses are usually progressive in their course, passing finally into coma and ending in death.

The largest number of cases of encephalopathia saturnina occurs in workers employed in the white lead industry.[15] It may occur in young adults in whom the urine is free from albumin and the brain removed at autopsy is chemically free from lead. According to Oliver cerebral hemorrhage is a common cause of death in lead poisoning.

The pathology of this syndrome-complex has been studied by a number of investigators. The general findings closely correspond to those of Case II in the present study. One of the best discussions of encephalopathia saturnina is that of Westphal[28] in 1888. He gives a careful review of the subject and presents the histological studies of the brains of thirteen of his own cases. Many of the brains showed no demonstrable lesions; some, however, showed small areas of hemorrhage, softening and atrophy. He found that the most important change was an inflammatory reaction around the minute bloodvessels. He believes that lead has a direct toxic effect on the nerve cells, though it is usually undemonstrable. He summarizes the effect of lead on the central nervous system as follows: (*a*) The direct toxic action on the nerve cells; (*b*) the toxic effect on the vessels, producing hemorrhage and encephalomalacia; (*c*) the effect on the kidneys resulting in uremic manifestations; (*d*) combination forms of the above three. Kussmaul and Maier[21] made one of the first careful histological studies of the brain in a case of encephalopathia saturnina and found very little characteristic except a mild periarteritis of the cortical vessels together with a slight perivascular increase of connective tissue. Monakow[11] describes a widening of the adventitia of the arterioles with an infiltration of cells, oil droplets and pigment granules. It is probable that the pigment granules are of the same type which were found by us. The ganglionic cells appeared pale and swollen. There was some atrophy and gliosis present. Steidle[29] states that anemia of the brain is the most common finding. Otherwise there is very little present to explain the action of the lead. He believes that even mild circulatory disturbances resulting from the toxic action of lead upon the bloodvessels are sufficient to produce profound functional disturbances, since ganglionic cells are so very susceptible to stimulation. He also emphasizes the direct toxic action of lead upon brain cells, since more lead has been found deposited in the brain than in most other tissues of the body.

Prognosis. The prognosis of the minor manifestations, including lead colic, is good; that of convulsions and other forms of the encephalopathies is usually serious. Wrist-drop and other types of paralyses may persist.

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restlessness and fits of melancholy. The chronic psychoses are usually progressive in their course, passing finally into coma and ending in death.

The largest number of cases of encephalopathia saturnina occurs in workers employed in the white lead industry.[15] It may occur in young adults in whom the urine is free from albumin and the brain removed at autopsy is chemically free from lead. According to Oliver cerebral hemorrhage is a common cause of death in lead poisoning.

The pathology of this syndrome-complex has been studied by a number of investigators. The general findings closely correspond to those of Case II in the present study. One of the best discussions of encephalopathia saturnina is that of Westphal[28] in 1888. He gives a careful review of the subject and presents the histological studies of the brains of thirteen of his own cases. Many of the brains showed no demonstrable lesions; some, however, showed small areas of hemorrhage, softening and atrophy. He found that the most important change was an inflammatory reaction around the minute bloodvessels. He believes that lead has a direct toxic effect on the nerve cells, though it is usually undemonstrable. He summarizes the effect of lead on the central nervous system as follows: (*a*) The direct toxic action on the nerve cells; (*b*) the toxic effect on the vessels, producing hemorrhage and encephalomalacia; (*c*) the effect on the kidneys resulting in uremic manifestations; (*d*) combination forms of the above three. Kussmaul and Maier[21] made one of the first careful histological studies of the brain in a case of encephalopathia saturnina and found very little characteristic except a mild periarteritis of the cortical vessels together with a slight perivascular increase of connective tissue. Monakow[11] describes a widening of the adventitia of the arterioles with an infiltration of cells, oil droplets and pigment granules. It is probable that the pigment granules are of the same type which were found by us. The ganglionic cells appeared pale and swollen. There was some atrophy and gliosis present. Steidle[29] states that anemia of the brain is the most common finding. Otherwise there is very little present to explain the action of the lead. He believes that even mild circulatory disturbances resulting from the toxic action of lead upon the bloodvessels are sufficient to produce profound functional disturbances, since ganglionic cells are so very susceptible to stimulation. He also emphasizes the direct toxic action of lead upon brain cells, since more lead has been found deposited in the brain than in most other tissues of the body.

Prognosis. The prognosis of the minor manifestations, including lead colic, is good; that of convulsions and other forms of the encephalopathies is usually serious. Wrist-drop and other types of paralyses may persist.

Prophylaxis. The most essential requirement among the workers in lead industries is cleanliness. Frequent bathing and thorough cleansing of the hands and finger-nails, especially before every meal, should be made obligatory. The air should be kept free from lead fumes and dust by proper ventilation. If with all possible precautions prevention for the individual is impossible then a change of occupation is necessary.

The use of leaden cooking utensils, cheap enameled dishes and food wrapped in lead-foil should be discouraged. Lead shot should never be used for the cleansing of bottles. Rigid laws should be enacted prohibiting the sale of lead-containing face powder, hair dye, lotions or any cosmetic containing a compound of lead.

Treatment. In the acute form the stomach is to be emptied by lavage. Epsom salt has antidotal properties and is the cathartic of choice.

In the chronic forms the treatment is principally symptomatic. Most authorities agree that iodide of potassium in small doses (5 to 10 grains), administered three or four times a day, aids in the elimination of the lead from the system through the kidneys and intestinal tract by transforming the insoluble salt as deposited in the tissues into a more soluble compound. However, it is to be used cautiously in the more acute forms, as the rapid liberation of the lead from the tissues may increase the severity of the intoxication. Epsom salt, castor oil and enemata are to be used for the relief of constipation. For the colic, cathartics, hot applications to the abdomen, amyl nitrite, atropin and sometimes morphin are indicated. Special attention should be given to the mouth for the relief of gingivitis and pyorrhea. Iron is indicated for the anemia. The paralyses should be treated by strychnin, electricity and massage. For the relief of convulsions many authors advise the use of baths, amyl nitrite and spinal drainage.

Summary. 1. Lead is the most important of the industrial poisons.

2. Women are more susceptible to lead poisoning than men; abortions, miscarriages and early deaths of the infants are common.

3. Lead is deposited in the liver, kidneys, brain and other organs.

4. Lead is eliminated principally through the urine and feces, but it may be absent in either even in the very severe forms of poisoning.

5. The kidneys in some types of lead poisoning show deposits of lime salts in degenerating tubules similar to that found in acute mercurial poisoning.

6. The lesions in the brain in cases of encephalopathia saturnina are not very prominent. The principal microscopic findings are a mild perivascular round-cell infiltration, satellitosis, neuronophagia and the occurrence around some bloodvessels of phagocytic cells containing a greenish crystalline pigment.

7. Basophilic granulation of the erythrocytes is a striking and characteristic feature of most cases of lead poisoning. With proper staining technic this finding is of inestimable value for diagnosis, and careful routine blood studies should be made as a prophylactic measure among the workers in industries using lead.

8. Besides being an industrial poison, lead is also the source of many miscellaneous forms of poisoning, chief among which is probably that resulting from the use of lead-containing cosmetics.

9. The use of lead-containing cosmetics over a prolonged period of time may result in death.

10. A face powder known as "Flake White" is lead carbonate ground to an impalpable powder. This powder is sold quite generally in drug stores for cosmetic purposes.

11. Mild degrees of poisoning from "Flake White" are probably widespread, but because the symptoms are often indefinite the true etiology remains undetected. Very severe cases probably also occur and remain undiagnosed.

12. The present study proves incontestably that death may occur from poisoning due to the use of "Flake White" as a cosmetic; it is very urgent, therefore, that rigid laws be enacted prohibiting the sale of any compound containing lead for cosmetic purposes.

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AN ANALYSIS OF ONE HUNDRED AND EIGHTY-TWO CASES OF CANCER OF THE STOMACH, WITH SPECIAL REFERENCE TO THE INCIDENCE OF PREËXISTING ULCER.

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Introduction. This study was undertaken with the idea of making available the data[1] that had accumulated during the last decade in this clinic on the subject of gastric carcinoma, and particularly in order to determine, in reference to the still unsettled question of the incidence of a preëxisting ulcer, the direction in which our evidence tended. Many of the facts brought out are already well established, and these will be passed over without special comment, although it is believed that they are of value in that they add something to the statistics of the subject; but on certain other matters that await their final solution we will refer to the literature and make such criticism as our findings seem to justify.

Preëxisting Ulcer. In presenting our data it will clarify matters to state at the outset that we have divided the cases into two groups: (1) Those giving a clinical history suggestive of a preëxisting ulcer, and (2) those of a progressive downward course without previous

[1] Most of the cases were studied on the medical service of the hospital, but some were admitted directly to the surgical wards, and for the privilege of including the latter we are indebted to the various surgical chiefs.

gastric symptoms. In the latter group it was usual for the patient to state, even in answer to leading questions as to ulcer symptoms, that he had never before had any digestive troubles. In the former we have included not only those giving a definite story of gastric upsets with more or less symptomless intermissions, but also those with any previous disturbance of the stomach except vague childhood affections. If we have erred, therefore, we feel that it has been by including too many in the ulcer-before-cancer group. There were, however, few borderline cases, most falling readily into the one classification or the other.

With even this liberality in making up our ulcer group, only 31 patients (17 per cent) of our total of 182 were so classified. It is appreciated that the relationship of gastric ulcer to gastric cancer must finally be established on a morphological basis, but as yet the pathologists themselves are not agreed upon the criteria which indicate this relation. In 1909 Wilson and MacCarty,[2] from a study of 153 freshly resected tumors which they believed to be malignant, concluded that 71 per cent of them were secondary to ulcer; later MacCarty[3] contended that 68 per cent of their gastric ulcers were associated with carcinoma, and Wilson and McDowell,[4] in an even more recent communication, stated it as probable that gastric cancer rarely developed except at the site of a previous ulcerative lesion. There has never been, however, a general acceptance of these claims of the members of the Mayo staff for the reason that others have questioned their interpretation of the specimens. Ewing,[5] furthermore, in an exhaustive study of the subject, with special reference to the criteria on which a judgment should be based, concluded that the cancerous transformation of peptic ulcer was rather infrequent and probably did not exceed 5 per cent. Also, Wilensky and Thalhimer[6] in a microscopical study of a series of benign and malignant ulcerations failed to trace an etiological relationship between gastric ulcer and gastric cancer.

On purely clinical grounds a similar diversity of opinion has developed. In 953 cases of gastric cancer Smithies[7] secured a history suggestive of a preëxisting ulcer in 66 per cent and Moynihan[8]

[2] Wilson, L. B. and MacCarty, W. C.: The Pathological Relationships of Gastric Ulcer and Gastric Carcinoma, Tr. Assn. Am. Phys., 1909, xxiv, 593.

[3] MacCarty, W. C.: Pathology and Clinical Significance of Stomach Ulcer, Surg., Gynec. and Obst., 1910, x, 449.

[4] Wilson, L. B. and McDowell, J. E.: A Further Report of the Pathological Evidence of the Relationship of Gastric Ulcer and Gastric Carcinoma, Am. Jour. Med. Sci., 1914, cxlviii, 796.

[5] Ewing, J.: The Relation of Gastric Ulcer to Cancer, Ann. Surg., 1918, lxvii, 715.

[6] Wilensky, A. O. and Thalhimer, W.: The Etiological Relationship of Benign Ulcer to Carcinoma of the Stomach, Ann. Surg., 1918, lxvii, 215.

[7] Smithies, F.: The Etiological Relationship Existing between Gastric Ulcer and Gastric Cancer, Illinois Med. Jour., 1917, xxxi, 149.

[8] Moynihan, B. G. A.: The Pathology of the Living and Other Essays, 1910, p. 109.

believed that two of every three of his cancer cases gave such a history. Deaver[9] has stated that he believed one-half followed ulcer and Mayo[10] has contended that in at least 50 per cent clinical evidence of a precancerous lesion, probably not always ulcer, could be obtained. It should be noted, however, that with the exception of Smithies none of these authors presented an analysis of cases to support the contention. On the other hand, Friedenwald[11] in an analysis of 1000 cases discovered a definite ulcer history in only 7.3 per cent, and in only 23 per cent had there been symptoms of any digestive trouble. Finally, it may be pointed out that the infrequency of cancer in the duodenum, where ulcer is common, argues against the importance of a preëxisting ulcer, as does also the fact that only rarely have proved ulcer cases while under observation developed malignancy. Thus there seems to be good reason to believe that our finding in this series of cases of only a small percentage of preceding ulcers is approximately correct.

Age, Sex and Color. The ages for the total series ranged from twenty-four to eighty-six and were grouped by decades as shown in Table I. It will be noted that 156 (85.7 per cent) were between forty and sixty-nine years old, this percentage being also correct for the sexes separately, and that about one-third of them were in the sixth decade alone. The two patients in the third decade were twenty-four and twenty-seven years of age respectively, one male and one female, and both were proved at operation. The age and sex incidence for the ulcer group was practically the same as for the total series. There were 139 males and 43 females. They were all white except two, who were negroes.

TABLE I.—THE AGE INCIDENCE BY DECADES FOR THE TOTAL SERIES AND FOR THE ULCER GROUP.

Ages.	Total series.		Ulcer group.	
	Number.	Per cent.	Number.	Per cent.
20 to 29	2	1.1	0	
30 to 39	14	7.7	3	9.7
40 to 49	46	25.2	9	29.0
50 to 59	61	33.5	11	35.5
60 to 69	49	26.9	7	22.6
70 to 79	9	5.0	1	3.2
80 to 89	1	0.6	0	
	182	100.0	31	100.0

[9] Deaver, J. B.: Early Recognition of Carcinoma of the Stomach, New York Med. Jour., 1919, cix, 749.

[10] Mayo, C. H.: Cancer of the Stomach and its Surgical Treatment (Collected Papers of the Mayo Clinic), 1919, xi, 41.

[11] Friedenwald, I.: A Clinical Study of One Thousand Cases of Cancer of the Stomach, Am. Jour. Med. Sci., 1914, cxlviii, 660.

Chief Complaint. Numerous chief complaints were stated by the patients, but by far the most frequent was that of pain in the epigastric region, this occurring 100 times (55 per cent). The next most common was that of vomiting, which was given in 31 instances (17 per cent). Others in the order of frequency were "stomach trouble," loss of weight, "indigestion," belching, "lump" in the abdomen, weakness, constipation and pain in the back.

Symptoms. *Pain.* Although only 55 per cent gave pain as the chief complaint, 161, or 88.5 per cent, stated it as one of the prominent symptoms. Of this number 152 (94.4 per cent) complained of its being in the epigastric region, while in a few it was localized in the back, the umbilical area, the precordia or the right shoulder.

The character of the pain was variously described. It was most often referred to as being dull (18 per cent), and next in order as a soreness, a burning, a gnawing, a heaviness, a cramp, a discomfort, an ache or a hunger pain.

Reference of the pain from its original localization was mentioned in only 51 instances, and it is interesting that in 25 of these, or about one-half, it was to the back. Of the latter the tumor involved the pylorus 20 times (80 per cent), the lesser curvature 3 times, the greater curvature once and the cardia once. The 20 pyloric cases with reference to pain to the back constituted 29 per cent of the total number with pyloric involvement. Reference elsewhere of the epigastric pain was not common, although it occurred in the sternal region 6 times, the left shoulder 5, the right shoulder 4 and the chest generally 4 times.

Relief from pain was noted in the series as the result of various circumstances in 85 cases. Most often, in 51 (60 per cent), it was accomplished by vomiting, in 11 by eating, in 5 each by belching, bowel evacuations and the application of local heat, and even less frequently by such measures as lying on the left side, making local pressure and gastric lavage.

Other Symptoms. The bowels were noted as being constipated in 67 of 150 cases and as markedly constipated in 56 more, that is in a total of 82 per cent. In most instances the constipation began at the same time as the other symptoms. In only 23 cases were they normal in action; in but 1 was diarrhea alone present, while in 3 diarrhea and constipation alternated.

The appetite was impaired in 153 of the total number (84 per cent) and 89 per cent complained of gaseous eructations. Vomiting occurred in 127 instances (70 per cent). Only 3 times, however, was hematemesis commented upon, and 2 of these were in the ulcer-before-cancer group. Nausea was noted 116 times, or in 75 per cent of the records in which it was referred to. The loss of weight averaged thirty pounds.

Duration of Symptoms. In presenting the duration of symptoms it is necessary to refer to the two groups of cases separately. In the 31 ulcer-before-cancer cases the average period of all gastric symp-

toms was 10.5 years, this corresponding closely with Smithies's[7] finding in his larger series of 10.8 years, whereas in 29 of the patients the symptoms which we interpreted as being due to malignancy averaged only 4.5 months. In the other 2 the history did not suggest any change in the symptomatology which might be explained as corresponding with a change in the histological picture. The average period of cancer symptoms in our complete series was 8.6 months, this again agreeing fairly well with the 6.9 months found by Smithies.

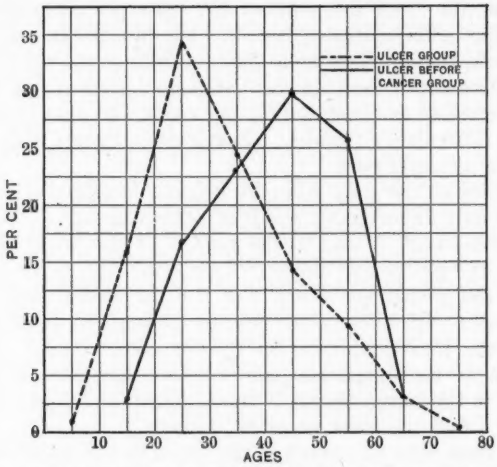

CHART I.—Age incidence for the beginning of "ulcer" symptoms in ulcer-before-cancer cases compared with that of ulcer cases at the time of applying for treatment. The latter is based on Friedenwald's findings in 1000 cases of gastric and duodenal ulcer.

Age Incidence for the Beginning of Symptoms. The age incidence for the beginning of symptoms in our ulcer-before-cancer cases (Table II) is noteworthy in that it shows that almost one-third of the total number fall in the fifth decade with as many in the sixth as in the fourth. No figures for the age incidence of the beginning of symptoms in benign ulcer are available in the literature, but even if comparison be made with the age incidence in such cases at the time of applying for treatment it will be seen that there is a wide difference. For instance, in Friedenwald's[12] series of 1000 cases, which is in agreement with other similar compilations, the acme of incidence, as shown in Chart I, occurs in the third decade. In his series the patients presented themselves at the clinic on the average of twelve years after the first symptoms were noted; thus the divergence of a curve that would represent the beginning of

[12] Friedenwald, J.: A Clinical Study of One Thousand Cases of Ulcer of the Stomach and the Duodenum, AM. JOUR. MED. SCI., 1912, cxliv, 157.

symptoms in his group from that of our ulcer-before-cancer cases would be much greater than this diagram indicates.

TABLE II.—AGE INCIDENCE FOR THE BEGINNING OF "ULCER" SYMPTOMS IN 31 ULCER-BEFORE-CANCER CASES AND IN 79 BENIGN ULCER CASES.

Ages.	Ulcer-before-cancer.		Benign ulcer.	
	Number.	Per cent.	Number.	Per cent.
10 to 19	1	3.2	8	10.1
20 to 29	5	16.1	36	45.6
30 to 39	7	22.6	21	26.6
40 to 49	9	29.1	6	7.6
50 to 59	8	25.8	7	8.8
60 to 69	1	3.2	1	1.3
	31	100.0	79	100.0

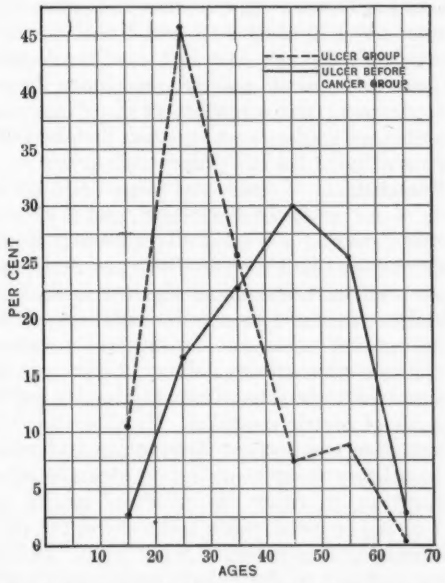

CHART II.—Age incidence for the beginning of "ulcer" symptoms in 31 ulcer-before-cancer cases and for the beginning of ulcer symptoms in 79 benign ulcer cases.

In order to secure accurate data on the age at the beginning of symptoms in ordinary ulcer cases we have gone over our benign gastric ulcer series (79 cases), and Table II shows, as would be expected, an even greater proportion of the cases between twenty

and thirty years of age. Comparison of the curve plotted from these cases with that of our ulcer-before-cancer group (Chart II) is consequently very striking. This suggests either that ulcers developing in later life have a greater likelihood of becoming malignant than do benign lesions generally or that the early symptoms are really those of a slowly developing malignancy.

Previous Medical History. The previous medical history of these patients, aside from gastric disease, seemed to have no bearing upon the diagnosis. Twenty-five had suffered from typhoid fever, 15 each from scarlet fever and pneumonia, 12 from gonococcal infection and lesser numbers from other infections. Six only (3 per cent) gave a history of trauma to the abdomen, this agreeing closely with Smithies's finding of 3.4 per cent., and being greater than Friedenwald's of 1.9 per cent.

Occupation. Likewise the occupation seemed unimportant. Thirty-three were housewives, all but 10 of the female patients, 19 were recorded simply as general laborers, 13 as farmers, 11 as miners, 8 as clerks and 7 as carpenters.

Family History of Cancer. The mother had suffered from cancer in only 8 instances: 1 in the breast and 1 each in the liver, face, bladder, uterus and stomach, and in 1 case the location was not stated. It had occurred in a sister three times (breast twice), a father twice (stomach) and a brother twice. This shows for our series a percentage of 8.8 for cancer in other members of the family, closely agreeing with the 9.4 in Friedenwald's group.

Physical Examination. A mass was palpated in the epigastrium in 95 patients of our series (52.2 per cent), and it was questionably felt in 16 others, making a total of 61 per cent. Emaciation was noted as being present in 151 cases (82.9 per cent), tenderness in 101 (55.5 per cent) and abdominal rigidity in 78 (43 per cent). Visible peristalsis was noted in only 30 instances. It is suspected that this finding does not represent the true occurrence of this interesting tell-tale phenomenon, since 42 per cent had pyloric involvement and 53.6 per cent of the 155 having gastric analyses showed evidence of gastric retention. Furthermore, this is a sign which requires close and patient observation and which is easily overlooked in a hasty inspection; but incidentally when found it is so significant as to repay the effort of careful examination. Enlargement of one or more lymph nodes above the clavicle on the left side was noted in 7 instances (3.8 per cent). In 3 of these the carcinoma was primary in the pyloric region, in 1 each along the lesser curvature and the cardia and in 2 it was described as being diffuse. In no patient were enlarged glands seen or palpated in the right supraclavicular area; such cases have, however, been reported and we have elsewhere encountered a few, though none happened to occur in this series.

Clinical Examinations. Most of the cases presented a moderate degree of secondary anemia, the extreme low figures being 20 per cent

of hemoglobin and 2,000,000 red blood cells. The average hemoglobin percentage was 61 (Fleischl) and the average red blood cell count 3,837,000. A leukocytosis (11,000 or more white blood cells) occurred in 31.2 per cent of the series while 11 per cent showed a leukopenia (under 6000), and 57.8 per cent had a count between 6000 and 11,000.

Urine and Feces. The urine showed albumin and casts in 86 cases (47.2 per cent). In 97 instances there were chemical studies upon the stools, but in only 52 of these (53.6 per cent) was there a positive reaction for occult blood. This is a smaller percentage than is given by some authors, and this is perhaps due to the fact that we were very careful to have our patients on a meat-free diet for several days before making the stool examination.

Stomach Analysis. The gastric analysis is of more importance. In the 155 of our patients who had one or more such tests the amount of the contents, removed forty-five minutes after an Ewald meal, was 100 c c or more in 53.6 per cent, 200 or more in 24.3 per cent, 300 or more in 13.6 per cent and 400 or more in 8.6 per cent. In 106 patients (68.4 per cent) there was no free hydrochloric acid, while in 7 (4.5 per cent) there was what generally has been considered a hyperchlorhydria (HCl above 40 $\frac{N}{10}$ NaOH). It was normal (20 to 40) in 22 (14.8 per cent) and there was a low hydrochloric acid content (0 to 20) in 20 (12.9 per cent).

Of the 27 cases that gave a history suggesting a previous gastric ulcer the figures were not notably different, 55.5 per cent showing achlorhydria, 7.4 per cent hyperchlorhydria, 18.5 per cent normal figures and 18.5 per cent hypochlorhydria.

The results of these analyses have also been grouped in reference to the position of the carcinoma and averaged as shown in Table III. The pyloric growths naturally gave rise to retention and coincident higher acid figures. When the cancer was situated at any other point the average content was about normal (except in lesser curvature involvement, which probably often produced some stenosis) and the acid figures decidedly and constantly subnormal.

TABLE III.—AVERAGE GASTRIC ANALYSIS FINDINGS ARRANGED ACCORDING TO POSITION OF THE TUMOR.

Position of growth.	Amount in c c.	Total acidity.	Free HCl.
Pylorus	213	45	10.5
Lesser curvature	207	16	5.3
Fundus and cardia	71	15	1.0
Greater curvature	68	15	3.0
Extensive	89	18	2.0

Wassermann Reaction. Although 3 patients gave a history of chancre, of the 83 Wassermann tests performed only 1 was positive. This patient (H. B.), aged thirty-seven years, giving a vague luetic history, was admitted on account of symptoms which suggested pyloric obstruction. The serological test was reported as 4-plus,

but the roentgen-ray study showed marked obstruction, and it was not thought possible to overcome this by constitutional treatment even if it were syphilitic. He was therefore operated on, a clinical diagnosis of carcinoma was made and a pylorectomy with gastroenterostomy done. Microscopic examination confirmed the diagnosis (adenocarcinoma). The patient rapidly improved, gained fifty pounds in weight and soon returned to his work as a gardener. Subsequently he was treated intensively with arsphenamin and mercury, but at the end of a year had a return of his obstructive symptoms. A second laparotomy revealed extensive abdominal metastasis.

Blood-pressure. Blood-pressure estimations were recorded in 119 of the patients, but in only 4 did the systolic reading exceed 160 mm. of mercury. The average systolic pressure was 118 and the diastolic 72. Curiously this is in complete variance with Friedenwald's finding of a systolic pressure above 170 mm. in 91 per cent of 132 cases.

Roentgen Studies. Roentgenographic reports were available in 125 of our cases and indicated that cancer was present in all but 4, thus giving the correct diagnosis in 96.8 per cent. In 3 the roentgenologist stated that the evidence he had was inconclusive, but suggestive of cancer; all of these proved to be inoperable when exposed by laparotomy. In a single case the roentgenological conclusion was incorrect, the operation showing carcinoma, whereas the diagnosis had been adhesions.

Operative Findings. Of the series 114 (62.6 per cent) were operated upon, but 3 of them at other hospitals. The percentage location of the tumors, as disclosed at operation, is presented in Table IV, and for comparison the location as determined by the roentgen-ray examinations. It will be noted that operation showed the pylorus and greater curvature involvements not to be so common as the roentgen-ray suggested, the excess being divided beween lesser curvature and diffuse lesions. This is about as would be expected, since when a lesion is on the lesser curvature the roentgen evidence of a filling defect is often on the greater curvature, and when extensive involvement is present only a part of it may be seen along the borders of the stomach.

TABLE IV.—PERCENTAGE LOCATION OF TUMOR AS DETERMINED BY THE ROENTGEN RAY AND OPERATION.

Position of tumor.	By roentgen ray.	By operation.
Pylorus	61.4	51.4
Lesser curvature	5.7	14.3
Fundus and cardia	10.0	10.0
Greater curvature	18.6	11.4
Diffuse	4.3	12.9
	100.0	100.0

Nature of the Operations. In only 28 per cent of the operated cases was any attempt made at radical removal of the malignant process; in 31.5 per cent the diagnosis was confirmed, but the condition was too far advanced to justify any surgical treatment, and in the remainder (40.5 per cent) only such a palliative procedure as would aid temporarily in the nutrition of the patient was undertaken. Mayo[10] reports that of 2094 operations for gastric cancer performed in their clinic between 1897 and 1919 there were 736 resections (35.1 per cent), 746 explorations (35.7 per cent) and 612 palliative procedures (29.2 per cent). Roughly it may be said, therefore, that only about one-third of all gastric cancers that now reach the operating table can be given any hope of a cure, while a second third may be made more comfortable and perhaps given an increased period of life. The other third receive no benefit whatever.

If it were possible to determine beforehand that those of the last group were definitely inoperable they could be saved the discomfort of the exploratory procedure. Carman[13] has emphasized the value of the roentgen ray in this respect, and it would seem that the latter has now reached such a point of perfection that it can be depended upon in the future to spare from operation a larger percentage of this group. Of even greater practical importance, however, is it that the second third, those who receive only palliative treatment, be more promptly diagnosed and referred to the surgeon.

The Non-operated Cases. Of the 68 patients not operated upon 38 (55.9 per cent) were considered inoperable. If this number is added to the 35 found inoperable upon exploration it gives a group of 73 patients (47 per cent of all the patients willing to be operated upon) in whom surgical intervention could be of no benefit.

Conclusions. This analysis of 182 carefully studied cases of cancer of the stomach leads to the following conclusions:

1. A history suggestive of preëxisting ulcer was obtained in only 17 per cent, and it seems probable that the true incidence of such a preceding lesion does not exceed these figures.

2. Reference of epigastric pain to the back occurred in 29 per cent of the pyloric cancers, and of those with reference of pain to the back 80 per cent had involvement of the pylorus.

3. The age incidence for the beginning of "ulcer" symptoms in the ulcer-before-cancer cases had its apex two decades later than did a series of 79 ulcer cases. This suggests either that ulcers first giving rise to symptoms in middle life have a far greater likelihood of becoming malignant than do ulcers generally or that the ulcer-before-cancer cases are really malignant from the beginning. Either of these considerations justifies and indicates prompt and radical surgical treatment of all patients first developing symptoms suggestive of ulcer after forty years of age.

[13] Carman, R. D.: The Operability of Cancer of the Stomach as Determined by the Roentgen Ray (Collected Papers of the Mayo Clinic), 1919, xi, 31.

4. The average free hydrochloric acid and total acidity findings in the pyloric cancers was not abnormally low (15.5 and 45), but there was evidence of definite retention. There was also retention in some of those with lesser curvature involvement. When the cancer was situated elsewhere retention did not occur, but the acid figures were distinctly low.

5. Roentgen study gave a positive diagnosis in 96.8 per cent, and in but one case was it misleading.

6. At operation the tumors were shown to be somewhat more extensive and more often to involve the lesser curvature than the roentgen ray suggested.

7. Of the patients with gastric cancer who now come to the surgeon about one-third are given a chance of cure by radical operation, one-third are treated palliatively and for one-third nothing can be done.

THE RELATION BETWEEN POLIOMYELITIS AND EPIDEMIC (LETHARGIC) ENCEPHALITIS.[1]

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In considering the relation between epidemic (lethargic) encephalitis and acute anterior poliomyelitis, much depends upon whether the subject is studied from the purely clinical aspect or from exact comparisons made with postmortem material. In each disease, however, careful examinations by both methods should be made before conclusions are drawn.

It is a firmly established fact that several types of exudative inflammations of the brain are infectious in character. It is not possible, however, from microscopic examinations of tissue alone, to separate with precision the alterations produced in the nervous system by each of the different known agents. True, certain individual cases have been recorded from time to time in which characteristic differences seem to be present, but when these points are analyzed carefully it can generally be shown that they are based chiefly upon the situation of the lesions or are apparent variations caused by modifications in the intensity and duration of the disease. They cannot, therefore, be regarded as characteristically different tissue reactions corresponding strictly and precisely to various infectious agents.

This opinion has frequently been expressed by different authors, and especially in regard to the practical impossibility of separating

[1] Read at the first meeting of the Association for Research in Nervous and Mental Diseases held at the New York Academy of Medicine, December 28 and 29, 1920.

the lesions of acute anterior poliomyelitis from those of epidemic (lethargic) encephalitis when examined under the microscope.

It is not surprising, therefore, that the clinical phenomena produced by epidemic (lethargic) encephalitis may resemble those of acute anterior poliomyelitis.

Prodromal Symptoms and Onset. Like the onset of acute anterior poliomyelitis, that of epidemic (lethargic) encephalitis is an exceedingly irregular one. Classifications of each of these diseases have been based upon the location of the structures paralyzed by the lesions in the central nervous system. From the studies made during epidemics by Wickman and others we learn that an abortive type of poliomyelitis in which paralysis is absent is frequently encountered, and thus our present conception that acute anterior poliomyelitis is an infectious systemic disease in which paralysis may or may not occur has become established. The number of cases of acute anterior poliomyelitis in which paralysis is absent varies considerably in different epidemics, but most observers agree that the abortive types represent about 50 per cent of all cases of the disease.

Comparing the onset and development of epidemic (lethargic) encephalitis, almost all recent observations show that the condition is related to a previous attack of influenza. Epidemic (lethargic) encephalitis is not, as a rule, a part of an attack of typical influenza, but it is a well-known fact that epidemic (lethargic) encephalitis may follow an attack of influenza. For this reason premonitory symptoms, or those preceding the development of paralysis in epidemic (lethargic) encephalitis, may be those of an infection or merely incidents in the convalescence from that disease. This stage of the disease, therefore, in which the symptoms resemble those of a chronic influenzal infection, represents the general systemic phase, which is exactly analogous to the abortive or non-paralytic types of acute anterior poliomyelitis. It may, however, progress and become a specialized expression in the form of an affection of the central nervous system with paralysis. In this respect the diseases run closely similar courses, and it seems unnecessary to quote here the details of cases showing no paralysis. For present purposes it is quite sufficient to refer to the fact that the differentiation of non-paralytic cases of acute anterior poliomyelitis, and of non-paralytic cases in which influenzal infection of the nervous system is suspected, is dependent largely upon the knowledge of the occurrence of an epidemic of acute anterior poliomyelitis or the prevalence of influenza or of epidemic (lethargic) encephalitis in the community in which the cases are observed.

The Bulbar, Pontile and Midbrain Form. Considered topographically there are certain well-recognized forms of acute anterior poliomyelitis in which the inflammatory process is well localized and reaches its greatest intensity in the cerebral peduncles, pons or

medulla oblongata, the spinal cord and cerebral hemispheres being unaffected. These are the cases that show the strongest resemblance to epidemic (lethargic) encephalitis. The weight of opinion, moreover, strongly favors the view that the polioencephalitis superior and inferior or the polioencephalitis of Wernicke is true influenzal encephalitis and merely modifications in type of the same disease.

Epidemic poliomyelitis is generally believed to occur during hot weather, particularly in July and August. Most of the victims are children and the lower-motor neuron type of paralysis is that most frequently encountered in cases with paralysis. The onset is sudden. Epidemic (lethargic) encephalitis is believed to occur chiefly during the winter months, the majority of cases having been met in adults. Not rarely a greater number of cases are seen in which only the cranial nerves are affected and there is prolonged lethargy, which is rare in acute anterior poliomyelitis. While such tendencies are important they are of no value in determining the nature of the disease in a given case.

Lethargy is not always present in cases of epidemic (lethargic) encephalitis; moreover, it occasionally occurs with acute anterior poliomyelitis. Tilney[2] has reported a case of acute anterior poliomyelitis in which it was severe and prolonged. Lethargy in various degrees, stupor or somnolence, frequently with delirium, may occur from intoxication in many different infectious processes, and while very common in epidemic (lethargic) encephalitis it is not in itself characteristic of the disease.

The clinical manifestations exhibited by lesions in the midbrain are most varied. Any extensive lesion in the bulb is almost invariably rapidly fatal, but the acute symptoms in both acute anterior poliomyelitis when it affects the bulb, as well as in epidemic (lethargic) encephalitis, may be severe. Nevertheless, they will often clear up, leaving a paralysis limited to one or more cranial nerves. In acute anterior poliomyelitis the seventh or facial nerve is said to be most frequently affected, whereas the third nerve is most often affected in epidemic (lethargic) encephalitis and also in Wernicke's polioencephalitis. Diplopia is therefore an early sign. However, any of the cranial nerves, as well as the limbs, may be paralyzed in each of these diseases from involvement of the pyramidal tracts from within the bulb. Neither the character of the paralysis of the individual cranial nerves nor combinations of types, such as unilateral, bilateral or multiple or single, have any significance in determining the etiology. These phenomena merely furnish indications of the locality of the inflammation and the direction and extent of its distribution.

In the cases recorded here, Case 1 was striking because of the slow onset, beginning with diplopia, due to involvement of the fourth

[2] Neurol. Bull., New York, January, 1918, i, 7.

and third nerves; numbness of the left lower limb, extending at times to the left upper limb and a tendency to fall to the left; nystagmus and scotoma, running a prolonged course. These symptoms indicated diffuse foci within the brain-stem—a myeloencephalitis resembling multiple sclerosis. The exact cause could not be proved, but because of the character of the onset, the slow and prolonged course and the absence of an epidemic of poliomyelitis, it seemed probable that the case belonged to the group included under the head of epidemic (lethargic) encephalitis.

During the recent epidemic of lethargic encephalitis cases resembling multiple sclerosis have been observed. Furthermore, the microscopic findings in some cases of epidemic (lethargic) encephalitis are identical in appearance to those seen in early cases of multiple sclerosis.

In Cases 2 and 3 the onset was sudden or apoplectiform in character, resembling, in this respect, bulbar poliomyelitis. The cause of the objective signs in each of these cases indicated an inflammatory process, at first acute and later assuming a chronic character. The paralyses were those of the motor cranial nerves and involvement of the pyramidal tract within the pons. These cases occurred in adults without spinal involvement, during a period in which epidemic (lethargic) encephalitis was prevalent. An epidemic of acute anterior poliomyelitis was known, however, to have been raging in the vicinity (Boston) in which Case 2 developed. These are regarded as cases of bulbar encephalitis of the poliomyelitic type, but whether they were due to the poliomyelitis virus or to that of epidemic (lethargic) encephalitis cannot be proved, though the former view seems most probable.

Cases of so-called influenzal myelitis have been observed by Spiller[3] and others.

A somewhat rare manifestation of acute anterior poliomyelitis is a transverse lesion of the spinal cord, the patient exhibiting complete flaccid paralysis of both legs, loss of sphincter control and absence of sensation up to the level of the lesion. The latter may remain complete or may clear up, leaving the patient with spastic paraplegia, with increased knee-jerk, defective control of the bladder, etc. It must be admitted that positive proof that such cases are caused by the virus of acute anterior poliomyelitis is often lacking, yet Batten[4] observed such cases during an epidemic of acute anterior poliomyelitis. B. Sachs[5] recorded a case of acute anterior poliomyelitis in a girl, aged eighteen years, with sudden onset of complete flaccid paralysis and loss of sensation up to the xiphoid cartilage; there was complete recovery in two months. The cerebrospinal fluid showed a high lymphocytic count.

[3] Arch. Neurol. and Psychiat., June, 1919, No. 6, i, 799.
[4] Brain, 1916, xxxix, 1 and 2.
[5] Jour. Nerv. and Ment. Dis., 1912, xxxix, 757.

Netter and Levaditi[6] reported four cases presenting symptoms of transverse myelitis which they attribute to the virus of acute anterior poliomyelitis. These authors were able to show that the blood of a patient who had recovered possessed the property of neutralizing the virus of acute anterior poliomyelitis.

I recently observed a similar case in an adult:

Mrs. M., aged thirty-seven years, previously healthy, in August, 1920, gave birth to a healthy child. There were no complications and she seemed to be entirely well. On September 30, on awaking in the morning, she experienced considerable discomfort in the back between the shoulders. This was soon followed by numbness, tingling and burning sensations, which increased in severity. The condition became very painful, extending throughout the trunk and the lower limbs, below the costal margin. Simultaneously her lower limbs rapidly grew weak. The next day she was completely paralyzed, both for sensation and for motion, below the level of the costal border, and retention of urine and of feces occurred. The temperature was 99.4° F. Lumbar puncture showed 150 lymphocytes to the cubic millimeter. Leukocyte count of the blood showed 10,000. She had severe pain throughout the anesthetic area, which subsided rapidly after lumbar puncture. On the fourth day her condition was greatly improved; motion was returning rapidly in both lower limbs and sensation was nearly normal. During the next five weeks only gradual improvement was observed. At the present time her spinal fluid is normal; sensation is restored and motor power is almost but not quite normal. There was a history of an attack of influenza one year prior to the onset and a chronic cough and pharyngitis that had persisted until within a few months preceding the onset of the present condition.

By some observers this case might be regarded as belonging to the group of conditions described under the name of the meningitic type of poliomyelitis.

In cases of epidemic (lethargic) encephalitis the spinal cord is not, as a rule, believed to be affected. In acute anterior poliomyelitis the spinal cord is involved much more frequently than other portions of the nervous system. At a meeting of the Philadelphia Neurological Society held in November, 1920, Winckleman and Weisenburg reported a very important case of epidemic (lethargic) encephalitis which they had observed clinically and at postmortem and found the usual evidences of that disease in the basal ganglia, reaching the greatest intensity in the pons and medulla oblongata. They also found intense perivascular infiltration and edema limited to the gray matter of the cervical and upper thoracic portions of

[6] Bull. et mém. soc. méd. des hôp. de Paris, 1914, xxxvii, 570.

the spinal cord. These alterations were identical in character and in location to those usually found in cases of acute anterior poliomyelitis, thus proving conclusively that in epidemic (lethargic) encephalitis the spinal cord may be affected.

A closely similar case is that reported by Harbitz:[7]

A woman, aged fifty-two years, following an attack of influenza, developed headache with partial loss of vision, first on one side and then on the other. The etiological factor was papillitis, resulting in complete blindness. Later both lower limbs became painful and weak and there was anesthesia as high as the axilla. The patient died of pneumonia. In the cervical cord segments so much congestion and edema were demonstrated that on cross-section the cord appeared grayish red in color, the boundaries between the gray and white matter being blurred. These changes were found with increasing distinctness in the first dorsal segment. Microscopic examination showed parenchymatous myelitis and neuritis, with degeneration of nerve fibers and ganglion cells in both the white and the gray matter. The resemblance of this case to the one referred to and reported by Winckleman and Weisenburg is very striking.

Local muscular atrophy is the one outstanding symptom of acute anterior poliomyelitis not observed in epidemic (lethargic) encephalitis, yet Grinker[8] refers to a curious case that he regards as a combination of acute anterior poliomyelitis and epidemic (lethargic) encephalitis. One year after having influenza the patient had an attack resembling apoplexy, with left-sided spastic hemiplegia. At first there were high leukocytosis and fever, transient sixth nerve palsy and strabismus, hyperemia of the optic nerves and muscular atrophy of the face and upper limb. Ten days later peripheral facial palsy followed the cerebral paralysis and there was atrophy of the muscles of the forearm and hand. The left thenar and hypothenar eminences resembled the Aran-Duchenne type of atrophy. Improvement occurred.

These observations tend to show that in epidemic (lethargic) encephalitis the extent of the inflammatory process is exceedingly variable and that the spinal cord may be affected. Spinal symptoms associated with bulbar signs do not therefore afford sufficient evidence on which to eliminate the possibility of epidemic (lethargic) encephalitis in diagnosis without consideration of the associated factors; neither does the absence of spinal-cord involvement lessen the probability of the bulbar symptoms being due to the virus of acute anterior poliomyelitis.

In concluding I would adduce the opinion that epidemic (lethargic) encephalitis is an infectious disease, having a separate

[7] Norsk. Mag. for Laegevidenskaben, January, 1920.
[8] Jour. Nerv. and Ment. Dis., October, 1920, No. 4, iii, 323.

and distinct entity that is not to be confused with acute anterior poliomyelitis, from which it differs particularly in the long survival of the virus in the central nervous system. Its course may therefore be very irregular and be attended with remissions or exacerbations extending over months or years. (See Case I.) The differential diagnosis between acute anterior poliomyelitis and epidemic (lethargic) encephalitis will often be impossible to make if only the subjective and objective signs are considered. Much will depend on the knowledge of existing epidemics and the weighing of circumstantial evidence afforded by the associated phenomena at the onset of the illness as well as before it develops.

The following records of cases are presented because of their resemblance to the two diseases under discussion and to illustrate the difficulties encountered in clinical diagnosis.

I wish particularly to thank Dr. Shumway for permission to refer to his cases (No. 1) and Dr. Spiller for allowing me to refer to Cases 2 and 3.

CASE I.—Miss W. H. W., aged nineteen years. Seen by Dr. Shumway.

The family and previous medical history are unimportant. The patient stated that she had been perfectly well until October, 1914, when she noticed for the first time that her right eyeball turned inward and that she saw double. This condition persisted. She did not feel sick, but had frequent attacks of nausea and vomiting. In March, 1915, while walking, she fell; she attributed this accident to her visual disturbance, but admitted that at times she felt unsteady while walking. Examination at this time by Dr. Shumway showed: The pupils were equal and reacted to light. Diplopia in the horizontal meridian, the right image being below and increasing downward and to the left, due to weakness of the right superior oblique muscle. Moderate but distinct nystagmus. Ophthalmoscopic examination revealed low-grade optic neuritis. In walking and standing there was a decided tendency to fall toward the right. The tendon reflexes on the right side were slightly greater than those on the left. The plantar reflexes and the sinuses were normal. The blood count showed: Red cells, 5,560,000; white cells, 6600; hemoglobin, 90 per cent. The Wassermann test of the blood serum and spinal fluid was negative, but there were 20 lymphocytes to the cubic millimeter.

Her condition remained about the same, with some increase in the ataxia; but in September, 1915, Dr. Shumway found marked bilateral central scotoma and nystagmus, with almost complete disappearance of the diplopia. The scotomata remained about the same, but with slight variations in size. Dr. de Schweinitz confirmed these observations.

The following findings were recorded by Dr. Spiller in September,

1918: Patient has had tingling and numbness of the left lower limb since last winter, but rarely in the right lower limb. At times it extends upward on the left side and involves the left upper limb. Occasionally her left knee gives way in walking. During the last two or three days she has had marked vertigo; if she looks downward, objects seems to be rushing by her, on both sides, with the speed of an express train. This occurs chiefly when she is walking. Has had frequent attacks of nausea since and before 1915. Headache not marked. Menstrual periods have been very frequent—about two weeks apart, and normal in character.

Pupils are equal—prompt reaction to light and in convergence. Nystagmus on either lateral movement—greater on looking to right. Patient wrinkles the forehead, closes the eyelids, draws up the corners of the mouth, either together or separately, contracts the masseters, protrudes and moves the tongue and raises the soft palate, all in a normal manner.

Touch and pain sensations normal in the face. The grip in each hand is good. Finger-to-nose test well performed on each side. Diadokokinesia not so well done with the left as with the right hand. Biceps and triceps tendon reflexes unusually prompt on each side, but equal. Stereognosis normal in each hand. Sense of position, passive movement, normal in each hand. Touch and pain sensations normal in each upper limb. Grasp is good and equal in both hands. No local atrophies. Patellar tendon reflex distinctly exaggerated and equal on both sides. No impairment of motor power in the lower limbs. Very distinct Romberg symptom—falls toward the left each time. Gait very unsteady with eyes closed and slightly ataxic with eyes open. Achilles tendon reflex a trifle more prompt than normal on each side. Babinski reflex is attended with no movement of the toes on either side. Touch and pain sensibility normal in the legs below the knees and feet. Position normal in the toes of each foot. Abdominal reflex not obtained on either side; no trace of any movement, either on stroking or tapping.

The chief symptoms consist of numbness in the left lower limb, extending at times to the left upper limb; tendency to fall to the left with eyes closed; exaggeration of all tendon reflexes; vertigo, nystagmus and findings in optic nerves mentioned by Dr. Shumway.

Case II.—August 23, 1920. Miss J. L. In perfect health previously; patient had returned shortly from a camp in Maine (?). On August 13, 1920, it was noticed that she was irritable and believed she was not well. That evening, at dinner, she suddenly declared that here eyes were "crossed"—she could not see properly—and complained of numbness in her right upper limb. She became profoundly stuporous, had a rectal temperature of 101⅗° and loss of control of the bowels and bladder, probably because of stupor. Doctor P. saw her about six days later. Her temperature

receded within a few days. About six or seven days after the onset the blood-pressure fell below 100; her breathing was of the Cheyne-Stokes type, but responded immediately to strychnin, which probably saved her life. Soon after the onset right hemiplegia was noticed.

"I found the patient stuporous, but she could be aroused and answered questions correctly, although a reply was secured with great difficulty. Her speech was very bulbar, not aphasic, and very difficult to understand. She had intense bilateral ptosis—could open the right lids slightly, but the left not at all. The left eyeball was entirely immobile; the pupil was widely dilated and did not react to light. The right eyeball had some downward and possibly a little upward movement, but no inward or upward movement could be detected. The left side of the face was normal. The right side was greatly but not completely paralyzed. She could draw up the right corner of the mouth in conjunction with the left, but probably not alone. The patient was too markedly stuporous to permit careful tests to be made. The wrinkles were somewhat fewer in the right forehead. The corrugator superciliæ functioned normally on each side. The soft palate moved normally. The tongue was red and coated, and when protruded, deviated markedly to the right. The right upper limb seemed completely paralyzed, but I was told that she had moved it slightly within a few days of my visit. The right biceps tendon reflex was nearly normal. A pin-prick caused discomfort in the right upper and lower limbs. A careful test of sensation could not be made because of the intense stupor. The right lower limb could be drawn up at the hip and the knees, but the patient had very little power. The right patellar jerk was feeble but the left was stronger. The Achilles tendon reflexes were uncertain. There was typical Babinski on the right side but not on left."

September 28, 1920. Patient keeps right eye wide open; no ptosis; right eyeball moves outward, downward, apparently inward, but not upward, but all movements except those of the upper lid are performed imperfectly. The right pupil contracts to light. Left ptosis complete—probably a little outward movement of the left eye, but no upward, downward or inward movement; no contraction of the left pupil to light. Innervates the right side of face a little when she shows her teeth. Does not speak a word. Frequent spasmodic movements, like those of crying, but there are no tears and no sounds. Right upper and lower limbs completely paralyzed. Right biceps and triceps reflexes a trifle more marked than the left. Right knee-jerks not very distinct but present, and not so good as the left; slight right ankle-clonus; distinct right Babinski but none on the left. Feels pin-prick in the right upper and lower limbs.

There is improvement in the general condition, marked by lessened stupor and increased appetite; no serious collapse has occurred for

three weeks; improvement in the right third nerve, but none in the left or right hemiplegia.

Considerable improvement subsequently occurred.

CASE III.—April 19, 1920. Professor H. Patient had been working very hard. Wife is tuberculous. She has had one pregnancy; no history of miscarriage obtainable. On March 31, while taking a shower-bath, the patient was discovered by his son leaning over, resting his head on the back of his hand, and seemed dazed. Dr. C. saw him an hour or so later; he stated that his face was much bruised, as though he had fallen. Both pupils dilated and left hemiplegia developed the same day. This has gradually improved.

The patient seemed unusually animated to Dr. P. a few days or possibly a week before the onset of the attack, and this fact was remarked on by Dr. P., but the patient's wife did not notice anything peculiar about her husband at that time. Examination showed bilateral ptosis equal on the two sides; palpebral fissures only about 2 mm.; right pupil dilated but not to the maximum; does not contract to light. Patient unable to look upward, inward or downward with the right eye; good outward motion and some slight fourth nerve action. Left eye impaired greatly in upward, inward and downward motion; left sixth nerve good. Complete right third nerve palsy; partial left third nerve palsy. Left pupil small but not excessively so; does not react to light. Weakness only of the lower part of the left side of the face; tongue protruded centrally; touch and pain sense in face normal. No rise of temperature at any time. Left upper limb freely movable at all parts, but distinctly weak; movements exceedingly incoördinate—more than the weakness justifies. Touch, pain, position and stereognosis normal on the left and right. Patient drags the left lower limb in walking and cannot walk without assistance. Left biceps and triceps reflexes diminished; left patellar and Achilles reflexes nearly normal. Typical Babinski on the left but not on the right. Touch, pain and position normal in the left foot.

Diagnosis: Vascular lesion or encephalitis of the right cerebral peduncle.

MENINGOCOCCUS SEPTICEMIA.

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THE occurrence of a septicemia caused by the meningococcus is becoming more frequently met with in recent years, and in the absence of a meningitis may easily be overlooked until the late

development of meningeal involvement gives the clue to the nature of the infection.

As a rule, these cases, particularly if left untreated, will eventually develop localizing signs either in the meninges, endocardium or joints, while if the character of the disease is recognized and specific serum treatment instituted at an early date these complications may frequently be avoided and a favorable outcome more often obtained.

Primary meningococcus septicemia is still comparatively infrequent, and despite the claims of some observers that all cases of epidemic cerebrospinal meningitis present an early bacteremia, the fact remains that when the case comes under the observation of the attending physician the signs of meningitic involvement are usually present.

Nevertheless, a primary meningococcemia may exist for weeks or even months, either with or without localizing signs, and, depending on the type of case, may closely simulate in its clinical course other acute infections, particularly malaria, acute rheumatic fever or endocarditis. The true nature of the infection may be revealed by the necropsy report, by the development of meningitis or by the demonstration of the organisms in the blood by means of blood cultures. The importance of keeping this fact in mind in atypical cases with doubtful etiology cannot be overestimated. The routine practice of taking blood cultures in these conditions should be insisted upon. The cultures should be taken repeatedly and over considerable periods, and should be incubated for at least seventy-two hours before being pronounced negative. Baeslack recommends that negative cultures be kept under observation for an additional five days before being discarded.

The Meningococcus intracellularis was identified in 1887 by Weichselbaum, who established its specific relation to epidemic meningitis.

The first case of meningococcus septicemia was reported in 1899 by Gwyn. This case was one of epidemic meningitis complicated by acute arthritis, and the meningococcus was isolated from the spinal fluid, the synovial fluid and the blood.

In 1901 the meningococcus was demonstrated in the blood of two meningitis patients by Cochez and Lemaire. Since that time meningococcus septicemia has been reported by Jakobitz, Martini and Rohde, Lenhartz, Marcovitch, Robinson and Duval. The meningococcemia in all of these cases was associated with meningitis.

In 1905 Elser, in examining the blood of 41 cases of cerebrospinal meningitis demonstrated the meningococcus in 10 of these cases. In most of these cases some form of extrameningeal lesion was present. The sites of these complicating lesions usually were the endothelial-lined cavities, such as the joints, the pleura, the pericardium and the endocardium.

Duval in his study of meningococcus septicemia makes the statement that no authentic cases are on record in which the meningococcus has produced lesions outside the meninges in the absence of preëxisting meningitis. However, we now know that the meningococcus may occur in the blood in cases in which there was no evidence whatever of preëxisting or accompanying meningitis.

The earliest case of primary meningococcus septicemia to be reported is that of Salomon, which occurred in 1902. This patient presented the symptom-complex of chills, fever and a profuse eruption resembling erythema exudativum. These symptoms continued for a period of about two months, at the end of which time the patient developed meningitis, the meningococcus being found in the spinal fluid. This patient finally recovered.

Andrewes, in 1906, reported a case of meningococcus septicemia who died in a few days and showed no evidence of meningitis either during the course of the disease or at autopsy.

Liebermeister, in 1908, reported a case of septicemia in which the meningococcus was demonstrated in blood cultures. This patient, after an illness of several months, finally recovered without ever having had any symptoms of meningitis.

Bovaird, in 1909, reported a case of meningococcus septicemia in which the spinal fluid was sterile. This patient's illness was complicated by severe iridocyclitis, but eventually ended in recovery after several injections of antimeningitis serum.

Cecil and Soper, in 1911, reported a case of meningococcus endocarditis and are inclined to favor the hematogenous route of infection in epidemic cerebrospinal meningitis.

Up to 1911 there appear to have been 5 cases of meningococcus septicemia reported in which there was no evidence of meningitis.

In 1915 Bray reported a case of meningococcus septicemia associated with pulmonary tuberculosis in which the patient recovered following the injection intravenously of antimeningococcus serum. He summarizes his case as follows: "The illness extended over a period of more than five months, with a known septicemia of three months' duration. The fifteen blood cultures yielded the meningococcus. The spinal fluid was sterile. The disease was characterized by a septic course, multiform eruption and cardiac murmurs, which later disappeared. The course of the infection was apparently not influenced by the administration of the serum." Bray's case received 260 cc of antimeningococcus serum intravenously during a period of twelve days. The initial dose was 20 cc and was gradually increased until the maximum of 40 cc was reached. He considered that the severity of the symptoms, together with the fact that the blood cultures still remained positive, suggested the advisability of discontinuing this form of treatment.

In 1917 Anderson reported 4 cases of meningococcus septicemia. These cases were apparently fulminating in type, showed a marked purpuric eruption and all resulted in death within a few days.

Sainton and Bosquet, in 1917, in discussing the clinical varieties of meningococcus septicemia, state that meningococcemia as well as meningitis may occur in such attenuated form that it may be unrecognized. They consider that one of the properties of the meningococcus is its ability to set up ephemeral disturbance in both the joints and the meninges.

In 1918 Sainton in discussing meningococcus infection of the blood describes seven different forms which this infection may assume, namely, the fulminating, the typhoid, the pseudomalarial, the eruptive, the articular, the metastatic and the abortive. He describes one case of meningococcemia in which meningitis developed on the sixty-ninth day. In the pseudomalarial form the patient may come and go freely during the period between attacks and thus sow the germ broadcast. Sainton considers intravenous injection of antimeningococcus serum to be the logical treatment, but recommends that great care be used in giving the serum intravenously, as this procedure occasionally proves fatal.

Netter in discussing intermittent fever of meningococcemia states that meningococcemia may assume the clinical appearance of typical intermittent fever, quartan or tertian. The attacks often coincide in such cases with the appearance of an eruption. In the majority of cases symptoms of cerebrospinal meningitis succeed these febrile attacks, but they may not appear for one or two months or more. Meningitis may even be absent altogether.

Krumbhaar and Cloud report three cases of fatal cerebrospinal meningitis with endocarditis. They emphasize the early occurrence of petechiæ as useful evidence in similar cases of septicemia.

Marino reports a case of meningococcus septicemia which died about nine hours after admittance to the hospital. He showed marked cyanosis and numerous hemorrhagic areas over the chest, the abdomen and the back, and blood cultures were positive for meningococcus.

Findlay, in 1919, reports a case of meningococcus septicemia without meningitis. The patient on admission presented a picture resembling the polyarticular type of gonorrheal rheumatism. He had a well-marked scarlatiniform rash on the thorax, the back, the face, the legs and the arms. Blood cultures were negative. Autopsy showed no evidence of meningitis, but smears from the serous exudate of the knee-joint and the pericardium showed the presence of the meningococcus.

Baeslack in a study of 25 patients suffering from meningitis demonstrated the meningococcus in the blood in 36.3 per cent of these cases. He concludes that systemic infection by the meningococcus is more frequent than previously suspected and that this systemic infection may occur without appreciable or with no localization. Also, he thinks that the systemic infection may be previous

to or coexistent with meningeal involvement, and therefore that the intravenous administration of antimeningococcus serum is rational and is indicated in conjunction with the intraspinal treatment.

Herrick believes that epidemic meningitis is preceded by a stage showing symptoms and signs of a generalized infection. This stage he considers lasts from a few hours to three days, averaging about forty-eight hours. A few patients with this meningococcus sepsis never develop meningitis. He states that these are usually either the abortive or the fulminating cases, rarely those with prolonged courses. He lays much emphasis on the skin manifestations in these cases. The milder types usually show a macular rash resembling early chicken-pox or large rose-spots. The predominating skin sign is the petechial rash. Purpura is a feature of the fulminating cases.

Renault and Cain in discussing meningococcus septicemia believe that purpura is a manifestation of septicemia and that the diagnosis can be made by cultivating the serous fluid from the purpuric lesion or by histological examination of a scrap of tissue from it.

Sergent reports a case of meningococcus septicemia which recovered after the intravenous injection of a stock vaccine of meningococci.

Lereboullet and Cathala report a case of meningococcus septicemia which at first was regarded as simple rheumatoid purpura but which a few days later developed fulminating meningitis. They emphasize the necessity of seeking for the meningococcus in every case of primary purpura.

Ribierre in discussing meningococcemia emphasizes the importance of identifying the exact strain of the meningococcus causing the infection in order that specific antiserum may be used. He advises five injections at twenty-four-hour intervals, alternating subcutaneously and intramuscularly. If improvement is not observed he then gives the serum intravenously. He considers that the patient should be kept under observation for at least a month after the supposed cure, as there may be a tardy relapse.

Blackfan in discussing the treatment of epidemic meningitis states that the intravenous administration of serum is indicated theoretically by the occurrence of a primary blood infection before the onset of the meningeal infection. As a rule, however, this occurs early and is a transitory invasion. The diagnosis at this stage of the disease is difficult to make and the vast majority of the cases are not recognized before the development of the meningeal symptoms. He states that after this time there is usually no bacteremia.

The following case of meningococcus septicemia without meningitis or endocarditis is reported:

CASE HISTORY.—Male, aged twenty-one years, white, unmarried.

Complaint. Headache, fever, drowsiness, lassitude, loss of appetite.

Family History. Negative.

Personal History. Measles in childhood; influenza in 1918, mild case, good recovery; influenza again in March, 1920, duration three weeks, good recovery, no complications.

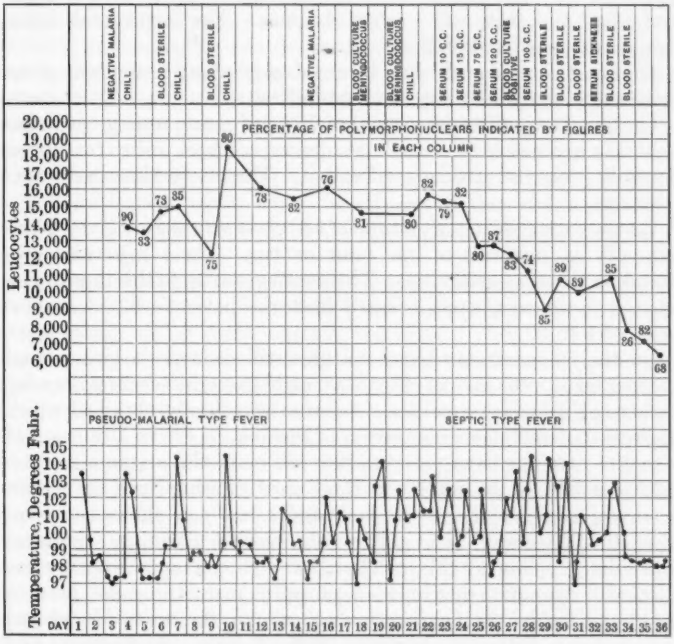
Present Illness. For a week prior to admission the patient felt tired and drowsy; had occasional headaches and poor appetite. Just prior to admission to the hospital the patient had a chill and severe headache.

Physical Examination. Upon admission to the hospital: Temperature 103.4°, pulse 104, respirations 24. The patient was well nourished and muscular. Color of skin and mucous membranes was good; no petechiæ. Lymphatic glands were not enlarged, spleen not palpable. Pupils were equal and reacted to light and accommodation; tongue slightly coated; tonsils somewhat hypertrophied but no angina present. Teeth in good condition; heart negative; lungs showed a few scattered rales at both bases. Abdomen soft; no tender areas or tumors; bones and extremities negative; reflexes, both superficial and deep, were normal. Eye-grounds negative; no muscular rigidity; no Kernig signs; no evidence of meningeal irritation.

Laboratory Data. Roentgen ray of chest negative; sputum negative for tubercle bacilli; throat cultures were repeatedly negative for Klebs-Loeffler bacilli and for meningococci. Blood smears were constantly negative for malarial parasites; blood cultures during the first two weeks of the disease were negative. The Noguchi reaction was negative. Stools normal and negative for ova or parasites. A complete record of the blood examinations is shown in the chart.

Clinical Course. On the day following admission the patient's temperature was normal and remained normal until the third day, when he had a chill and his temperature rose to 103.4°, followed by a profuse sweat and a return to normal temperature. Seventy-two hours later the patient had a similar chill, the temperature rising to 104.2°, returning to normal the next day. This quartan type of temperature continued during the first two weeks, following which the temperature assumed the septic type with a tendency to approach normal in the mornings and with an evening rise to 102° or 103°. The type of temperature in this case is shown in the chart. The leukocyte count during the first two weeks varied from twelve to eighteen thousand, with approximately 80 per cent of polymorphonuclears. Following the second chill on the fourth day after admission several spots appeared on the skin which were slightly raised, hyperemic, pale rose in color and irregularly distributed over the upper chest, the legs and the arms unaccompanied by itching, and which tended to disappear during the apyretic periods. This eruption resembled very much the rose spots of typhoid fever.

The eruption would sometimes persist for a day or two, then disappear completely and reappear again at irregular intervals. It was noticed first on the fourth day and persisted up to the third week. On the tenth day there was some swelling and tenderness of the right knee, which disappeared in twenty-four hours. On the twelfth day the patient complained of soreness of the fingers and the left wrist, which persisted for one day. On the days the temperature remained normal, the patient was much improved, had no discomfort, appetite was good and there was a general feeling of well-being. During the second week the patient developed marked



herpes labialis. There were no localizing signs or symptoms during the course of the disease, except the ephemeral joint disturbances, no evidence of meningeal irritation, and repeated blood cultures were negative up to the eighteenth day of the disease, when a Gram-negative diplococcus was discovered. The temperature chart, which strongly suggested a quartan malarial infection, led to repeated search for malarial parasites, although the blood picture, showing a moderate leukocytosis and an increase in the polymorphonuclear cells, was distinctly against a malarial infection. However, on the ninth day quinin was administered by the mouth in ten-grain doses, three times a day for a period of five days, without noticeable effect.

On the eighteenth, twentieth and twenty-first days blood cultures showed the presence of a Gram-negative diplococcus which conformed in all respects to the meningococcus, both culturally and serologically. This organism was agglutinated by polyvalent antimeningococcus serum and by Type IV Gordon serum. It was also identified as a meningococcus by the Naval Medical School and the Public Health Laboratories at Washington, D. C.

On the twenty-third day serum treatment was commenced, ½ cc of polyvalent antimeningitis serum being given subcutaneously, and two hours following this 7 cc were given intravenously At this point the patient became slightly cyanotic, the pulse became rapid and small and there was evident dyspnea. The intravenous injection was stopped at this time.

On the twenty-fourth day 15 cc of polyvalent serum was given intravenously without any untoward effect.

On the twenty-fifth day a total of 75 cc of serum were given intravenously in doses of 15 cc each, at intervals of from one to two hours, depending on the patient's condition. These injections were well tolerated.

On the twenty-sixth day a total of 120 cc of serum were given intravenously at intervals of one hour or two. These injections produced no alarming symptoms. The serum given up to this time agglutinated the meningococci isolated from the patient's blood in dilutions of 1 to 50.

On the following day blood cultures still showed the presence of the meningococcus and an effort was made to secure serum possessing higher agglutination qualities. A serum was finally obtained which agglutinated this particular strain of meningococcus in a dilution of 1 to 400. On the twenty-eighth day 100 cc of this serum was given intravenously by the gravity method after diluting three times with a normal saline solution. An hour and a half was allowed to complete this injection. The patient showed no alarming symptoms immediately following this injection, but eighteen hours later became markedly cyanotic, developed a purpuric rash, the pulse became rapid and feeble, the temperature subnormal, the heart dilated and the condition distinctly alarming. Following the use of atropin and digitalin hypodermically these alarming symptoms gradually subsided, the temperature rose to 101° and the patient about six hours later was in good condition.

On the thirtieth day the temperature was 103°, the pulse 112 and the respirations 24, and it was not considered advisable to continue the further use of serum at this time, particularly as blood cultures following the last injection of serum were negative.

On the thirty-first day the temperature remained normal, the pulse 92 and the respirations 20. The leukocyte count was normal at this time and the blood culture was negative. From this point on the patient made constant gains and repeated blood cultures were negative.

On the thirty-second day the patient developed serum sickness, nine days following the first administration of the serum. He showed the typical urticarial lesions of serum sickness, which persisted for about twenty-four hours and then disappeared. From this point on the patient made a rapid and uneventful recovery and two months later showed no evidence of his former illness.

There was no evidence of an endocarditis at any time during the course of the disease, and with the exception of the evanescent arthritis of the knee and wrist there was nothing to indicate a localizing lesion. At no time during his illness did the patient show evidence of meningitis or meningeal irritation. A spinal puncture was not performed for two reasons: the first being the absence of all signs pointing to meningitis, and the second the danger of introducing the meningococcus into the spinal canal while the patient showed the presence of the organism in the blood stream. Although it has been urged by some observers that a prophylactic injection of antimeningitis serum into the spinal canal might prevent the development of meningitis, it was considered that the intravenous method of administration, while more directly combating the septicemia, would at the same time act as a prophylactic against meningeal infection.

During the acute course of the disease the patient showed evidence of renal irritation, as evidenced by the presence of albumin and occasional hyalin and granular casts in the urine. These, however, disappeared following the return of the temperature to normal, and the urine one month later was negative.

As to the best method of administering serum in meningococcus septicemia it would appear that the frequent intravenous injection of small amounts of serum, say 15 c c to a dose and repeated at intervals of an hour or two, depending on the patient's condition, are preferable to the single injection of a large amount of serum, as the alarming symptoms following the injection by the intravenous method may frequently be delayed, whereas if the injection be given in small doses, waiting a few hours between each injection, the chances of overwhelming the patient before the serum injections can be stopped are greatly lessened.

It is believed that this principle would apply with equal force in the administration of other specific sera and that many of the untoward effects could be avoided by this procedure.

This case may be summarized as follows:

It began as an acute febrile condition with a temperature chart typical of quartan malaria but with a moderate leukocytosis and an increase in the percentage of polymorphonuclears, and at the end of the second week the temperature became distinctly septic in type. A maculopapular eruption, resembling the rose spots of typhoid fever, appeared on the fourth day and persisted up to the third week. There were no localizing signs at any time during the course of the

disease except the transient joint symptoms. Blood cultures were negative up to the eighteenth day when the meningococcus was identified. He received a total of 320 cc of antimeningococcus serum intravenously over a period of six days, following which the temperature became normal and the blood cultures sterile. Recovery was uneventful from this point. The prompt termination of the febrile course, the marked improvement in the general condition of the patient and the negative blood cultures following the specific serum therapy leave no room for doubt regarding the efficacy of this form of treatment.

It would appear that cases of meningococcus septicemia are becoming more frequent, or at least more frequently recognized, and that it is well to be on the alert for such cases in order that the diagnosis may be made and treatment instituted before the development of meningitis or endocarditis. The appearance in an acute febrile case of petechiæ or a maculopapular eruption resembling at times the rose spots of typhoid fever, together with a moderate leukocytosis and a temperature chart, which may either be of the septic type or may resemble markedly the chart of malarial fever, should raise the suspicion of meningococcus sepsis and should lead to repeated blood cultures being made in an effort to identify the meningococcus. The skin lesions of meningococcus sepsis are particularly striking. The eruption may be purpuric, hemorrhagic or maculopapular. In the acute fulminating cases, which usually die within the first few days, a purpuric generalized eruption is the rule. These cases are quickly overwhelmed and die frequently before the development of meningitic symptoms. In the protracted cases of meningococcus sepsis the character of eruption shows more of a tendency to assume the maculopapular or hyperemic type.

Some observers lay great stress on the intravenous administration of serum in acute meningitis and are of the opinion that the organism gains entrance to the meninges through the blood stream, thereby inferring that all cases of meningitis are primarily bacteremias. While it is true that positive blood cultures can be obtained in a fairly large percentage of cases of meningitis the fact also remains that the average case of cerebrospinal meningitis has well-developed meningitic symptoms at the time he comes under the observation of the physician. Acute primary meningococcus sepsis without involvement of the meninges is still a rare condition, and while these cases, if untreated, as a rule, will develop a meningitis in the course of a few weeks or months, their early recognition by means of blood cultures will usually serve to prevent the development of meningitis by the early administration of adequate serum therapy.

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THE MORPHOLOGY OF THE HEART IN RELATION TO HABITUS AND A NEW METHOD OF ESTIMATING MORPHOLOGICAL CHANGES. A ROENTGEN STUDY.[1]

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The older teaching of visceral morphology based on the anatomical findings in the cadaver have given way to a newer and truer conception based on the roentgen examination of the living.

Roentgenology has demonstrated that there exists no one type of organ as regards morphological characteristics, and as far as morphology influences function, there is no one type of physiological normal.

It was the organs of the gastro-intestinal tract which were first considered in the light of this conception, for the roentgen examinations soon demonstrate that in contrast to the previous anatomical teaching there was no one type of stomach as regards its form, shape, outline, axis, mobility and physiological activity, but that the morphological and to a certain extent the physiological characteristics depended very greatly on the body cavity which housed them. In other words the morphological normalcy of an organ depends on its conformation to the type of organ which belongs to the particular habitus. This from a modern viewpoint is the basis for the establishment of the normal.

The organs of the thorax must also be studied in the light of this conception of the variation in visceral morphology with bodily habitus.

In the roentgen-ray department of Bellevue Hospital the classification of Mills of the four major types of general physique has been adopted and in use for several years. These major types are the hypersthenic, the sthenic, the hyposthenic and the asthenic.

Characteristics of the Major Types. The asthenic habitus is one which presents the following anatomical thoracic characteristics: The thorax is long, shallow and narrow. The subcostal angle is very acute. The ensiform is usually absent. The pulmonic fields are relatively broad in the upper part and narrow in the lower, with large apices which extend well above the clavicle. The diaphragm slopes sharply downward. The relationship of downward inspira-

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tory movement to upward expiratory movement in forced respiration is as 1: 5. The abdomen is relatively short. The diaphragms are flat. They are at the level of the eleventh rib. The transverse pelvic diameter is much greater than the chest transverse diameter at the base of the thorax.

In the hyposthenic habitus the thorax is only moderately long but somewhat broader than in the above type. The subcostal angle is wider, being about 40 degrees. The pulmonic fields are not so narrow at their bases. The domes of the diaphragm slope downward. They are at the level of the tenth rib. The relationship of downward inspiratory movement to upward expiratory movement in forced respiration is as 1 : 3. The disproportion between the pelvic diameter and that through the base of the thorax is not so great, but the pelvic diameter is still wider.

In the sthenic habitus the thorax is shorter and wider. The subcostal angle is about 90 degrees. The pulmonic fields are relatively wide at the base and narrow in the upper zone. The diaphragmatic domes show even convexity. They are at the level of the ninth rib. The relationship of downward inspiratory movement to upward expiratory movement in forced respiration is as 1 : 2. The pelvic and thoracic diameters are approximately equal.

In the hypersthenic habitus the thorax is short, its anteroposterior diameter is great and the subcostal angle is very obtuse. The pulmonic fields are very broad in their lower zones. The apices scarcely show above the clavicles. The diaphragmatic domes are convex and high. The right is at the level of the eighth rib. The downward inspiratory movement is to the upward expiratory movement in forced respiration as 1 : 1. The transverse thoracic diameter is greater than the transverse pelvic diameter.

Heart Morphology in Relation to Habitus. In the roentgen study of the heart in the light of habitus the cardiac shadow must be studied in relation to the pulmonic fields in which it is located. The pulmonic fields are two triangular areas shaped like Gothic windows, bounded below by the curve of the diaphragm and above and laterally by the convergence of the ribs, and correspond to the areas occupied by the lungs.

The characteristics of the pulmonic fields—namely, the altitude, the transverse diameter at the level of the domes and the degree of curvature of the diaphragmatic domes—are expressions of the habitus, for each habitus possesses characteristics as regards the transverse diameter, altitude and basal curve, which are peculiar to it. So, also, the changes which are produced in these factors during the respiratory phase are peculiar to the particular habitus. For instance the altitude of the pulmonic field increases during inspiration. It increases more in the hypersthenic and scarcely changes at all in the asthenic even in forced inspiration. Thus in the sthenic, in the vertical posture the diaphragm moves twice as

far upward in expiration as it does downward during inspiration; in the hypersthenic the relation of upward to downward displacement during respiration is equal and in the asthenic there is five times as much upward displacement during expiration as there is downward displacement during inspiration, but the sum total of movement is less than in the higher types.

There is also a similar variation in the transverse measurement during respiration and the degree of variation differs in the different habiti.

The most striking changes during respiration, however, are in the position, the degree of curvature and in the variation in shape of the diaphragmatic domes. And these changes differ in the various forms of bodily habitus. The intimacy of the anatomical relationship of the heart to the diaphragm is such that in the morphological study of the heart, the diaphragm becomes perhaps the most important factor to be considered.

Position of the Heart. There exists an intimate relationship between position of the diaphragm and the position of the heart. In order, therefore, to study the position of the heart in the particular habitus it is essential that the study be made with the diaphragm in a certain standard position. It is, of course, impossible to obtain by a maneuver a relatively similar position of the diaphragm in the various habiti. It is, however, essential for the purpose of comparison that the variation in the different types be as little as possible. To that end the position of the heart in all the types, except the asthenic, is studied in deep inspiration. In the latter type the heart is studied in deep expiration.

In the asthenic type, where the diaphragm is low, the heart position differs strikingly from that in the hypersthenic type, where the diaphragm is high. In the hypersthenic the heart lies "transversely," the axis being relatively horizontal, about 33 degrees (the angle formed by the intersection of the transverse and long diameters). In the sthenic type the heart lies "somewhat obliquely," the axis having an obliquity of 37 degrees. In the hyposthenic type the heart is "markedly oblique," the angle of the heart axis being 43 degrees and in the asthenic type the heart is "vertical," the angle of the heart axis being 48 degrees, but may be as much as 55 degrees.

It is thus seen that so far as the axis is the expression of position, the heart varies in its position according to habitus.

Form of the Heart. The heart is generally described in the anatomies as being conical in form. The roentgenological studies of the living have shown that grossly the heart shape varies distinctly. This variation in heart form is due primarily to the developmental factors which produce the habitus, but is undoubtedly also influenced in some degree by the physiological requirements of the body activity which includes degree of nutrition and skeletal muscular development. Nevertheless, the predominating factor is habitus.

The heart shape in the hypersthenic habitus is broad transversely, relatively short vertically and generally oval. The cardiovascular angle is obtuse, 135 degrees, and distinct. The left ventricular curve shows considerable convexity. The apex is broad and points outward (Fig. 1).

The heart shape of the sthenic habitus is triangular. The cardiovascular angle is distinct, having a value of 150 degrees. The curves of the right auricle and left ventricle are only moderately convex (Fig. 2).

FIG. 1.—Radiograph—the chest of the hypersthenic habitus.

The heart shape of the hyposthenic habitus shows a tendency to circular form. The cardiovascular angle is about 165 degrees and is displaced to the upper part of the median shadow. The curves, particularly the left ventricular, are less convex than the sthenic (Fig. 3).

The heart shape of the asthenic habitus is long and narrow, approaching a circular form. The cardiovascular angle is obliterated, so that the upper half of the left heart border is almost a straight line. The curves of the right auricle and left ventricle show comparatively little convexity. The apex points downward and is

sharp (Fig. 4). It is thus apparent that the convexity of the various curves which constitute the heart silhouette varies with the habitus and that the heart shape as a whole varies in form with the habitus.

Size of the Heart. The most commonly utilized measurement of the heart is the transverse diameter. This is obtained by drawing perpendiculars from the median line to the point of maximum deviation of the heart shadow to the right and to the left, the sum total

FIG. 2.—Radiograph—the chest of the sthenic habitus.

of which is spoken of as the maximum transverse diameter. Numerous tables of this sort have been devised, by Groedel, Moritz, Otten, Dietlen, Bouchard, Guillemont, Claytor and Merrill, for the upright, sitting and horizontal postures, and the posture, age, height, weight, sex and occupation have been utilized as factors in the estimation of the size of the cardiac shadow, and normal limits have been tabulated.

The analysis of these tables and our own studies would indicate that age, sex and height are relatively unimportant factors in the estimation of the heart size.

For instance, take the compilation according to height. For a heighth of 66 to 69.6 inches the variations (horizontal) of the trans-

verse diameter (Dietlen) are 11.3, 13.1, 15.3, a variation of 4 cm. Sitting (Groedel), 11.4, 13.2, 14.6, a variation of 3.2 cm.

Thus the heart in an individual of this height might if his transverse diameter were 13.3 be either 2 cm. too small or too large and if 15.3 might be 4 cm. too large or normal (Haudek).

Further, in Groedel's tables a male individual of 58 to 61.6 inches may have a transverse diameter of 12, 13.1, 14.4 while a male of 70 to 74 inches (a foot higher) may have 12, 13.2, 13.6, the average measurement increasing 1 mm. while the maximum is less for the

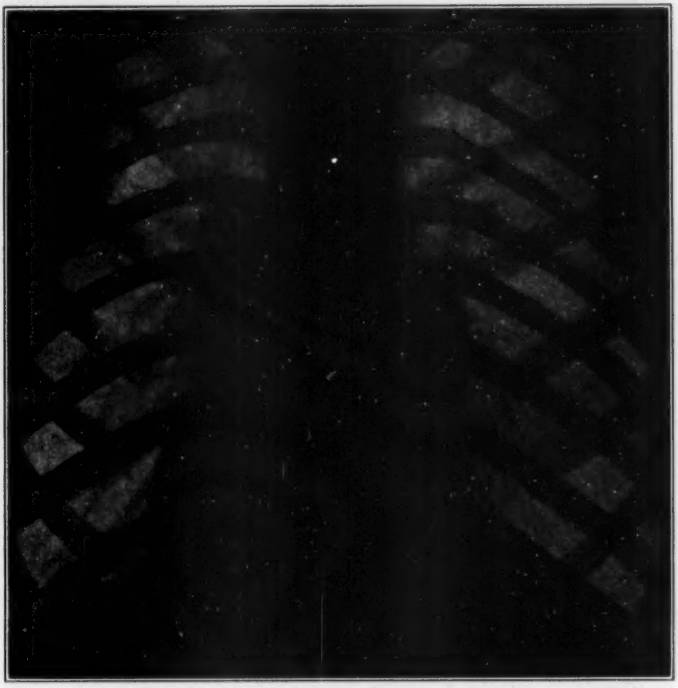

FIG. 3.—Radiograph—the chest of the hyposthenic habitus.

taller man. There is still less variation in the measurements made in the standing position. So, also, in Smith's figures the difference in transverse diameter measurement between a man 60.2 and 72.2 inches is but 7 mm.

To still less a degree does sex and age vary the transverse measurements. Weight better than any of the other factors permits a classification in which the differences appear to be more consecutive in the average. This is because weight is in a sense a characteristic of habitus, for the weight averages highest in the hypersthenic and lowest in the asthenic, yet in Claytor and Merrill's tables, arranged

according to weight, the minimum T. R. of a man weighing 120 to 129 pounds is given as 10.7 and the minimum T. R. of a man weighing 180 to 200 pounds is given as 11.0, a difference of 3 mm.

There is another and more weighty criticism of these standard measurements, and this is that, depending on the axis of ovals of identical shape and size, there will be a variation in the maximum transverse diameter as obtained in the usual method of measurement of this diameter (Fig. 5). It is therefore possible for two indi-

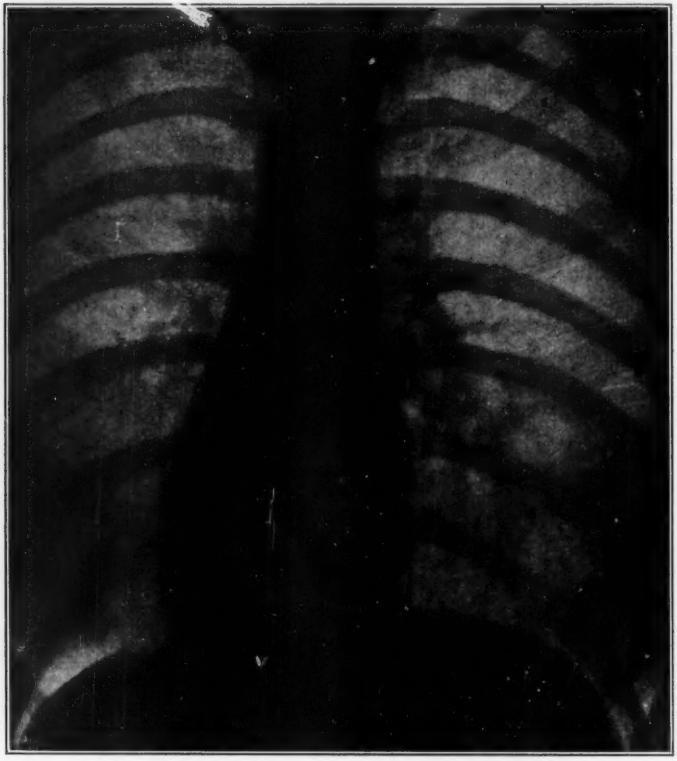

FIG. 4.—Radiograph—the chest of the asthenic habitus.

viduals to possess the same-sized hearts, but in one case, if housed by a hypersthenic thorax, the maximum transverse diameter will be greater than if the same heart were housed in an asthenic thorax.

This transverse measurement, therefore, must be balanced against the angle of obliquity of the heart axis to be of any clinical value, and as a further check the other expressions of habitus, the altitude and the width of pulmonic field must also be taken into consideration, and still further the possible influences which variations in weight may exert must be noted. It is therefore logical to deduce

that the transverse or for that matter any of the standard measurements are only of value when considered in the light of habitus.[2]

Taking the factors given, the value of the angle of obliquity of the axis, size of pulmonic field and weight, in consideration, it is

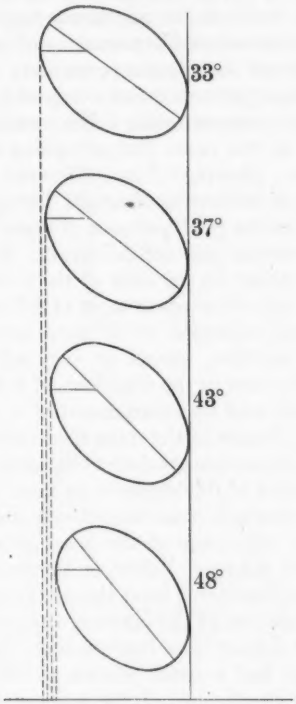

FIG. 5.—Showing the variations in transverse measurement of the same oval in various degrees of obliquity.

possible to establish sets of figures which express heart size in a fairly rational manner (Table I). Haudek has established tables in which there is a decided increase in the various subdivisions of the average values from 2 to 2.2 cm., but he does not consider them from the standpoint of habitus and its dominant types.

TABLE I.—AVERAGE STANDARD MEASUREMENTS IN RELATION TO HABITUS.

	Transverse diameter.	Long.	Broad.	Aortic arch.
Asthenic	8.8	11.4	9.9	3.9
Hyposthenic	11.1	13.1	10.6	4.8
Sthenic	12.4	14.1	10.6	5.1
Hypersthenic	13.8	14.7	10.7	5.7

[2] The clinician, then, when he maps out the heart in relationship to the nipple and midclavicular line, and in reference to the interspaces and ribs, is correct, for he is determining the relationship of the heart to the habitus. But he must view the estimation from this standpoint.

But when all is said and done, when the figures are studied, even with the checks enumerated, one is driven to the conclusion that though the roentgen estimation of the cardiac diameters can be made with more actual accuracy than by clinical methods, nevertheless its greatest value is not so much as an absolute measurement, but that it serves as a check on the percussion findings of the clinician rather than as an anatomical determination of cardiac size. Dietlen examined 231 patients with finger percussion, medium stroke and firm pressure of the pleximeter and compared his findings to the orthodiagrammatic measurements. His conclusions are that in three-quarters of all the cases the percussion findings correspond to the orthodiagram, allowing 0.5 cm. difference. De la Count finds percussion correct in estimating the right border in 85 per cent. of cases and the left border in 70 per cent of cases, allowing 0.5 difference between percussion and orthodiagram. It must therefore be concluded that in about 75 per cent of the cases the heart can be correctly mapped out, allowing an error of 0.5 to 0.75 cm.

The main general objection to all these standard diameters is that they do not indicate, except in very advanced lesions, the changes which take place in the chambers of the heart. A thickening of the heart wall and an enlargement of a heart chamber may occur without any change in the numerical value of the diameters. But such changes will at once produce a change in contour and shape, and the determination of this seems to be more important than the numerical values obtained from the various diameters.

Now the various chambers of the heart produce curves in the contour of the heart shadow. Below, on the right side, we have the right auricular curve springing from the diaphragmatic shadow and extending to the junction of the curve of the ascending arch of the aorta. On the left side we have four curves. The uppermost is the curve of the arcus and a small portion of the descending arch. This is overlapped by the arc of the pulmonary artery, which is overlapped below by the curve of the left auricle, the latter two curves being located in a valley, situated between the high points of the arcus above and the left ventricular curve below, which extends from the left auricular curve to the diaphragm where it merges with the right ventricular curve.[3]

An estimation of the relative size of the heart chambers can be obtained with a fair degree of accuracy by the determination of the convexity of the curve which constitutes the profile of the chamber and actual measurements indicate that the values of the curves vary with the habitus.

[3] Radiographically the determination of some of the points of division of the cardiac shadow corresponding to the junction of certain chambers of the heart is simple, as in the right auricular curve or in the pulmonic curve, but at other points, as for instance between the right and left ventricles and between the left auricle and ventricle, recourse must very frequently be had to ortho- or telefluoroscopic methods. It is important to determine this latter point, which marks out the base of the heart, at which ventricular contractions cease—a point of no motion.

The cases used for the study were patients from the wards of the third surgical division, Bellevue Hospital, and medical students from the University and Bellevue Hospital Medical College. They were regarded as normal, following a careful history and a thorough physical examination, particularly as regards their abdominal and thoracic viscera and peripheral circulation.

The relationship of cardiac size, form, position and function to each type of habitus was then studied by all the roentgen methods.

The following technic and routine were employed in fluoroscopy. The examination was made in all positions and postures with fluoro-

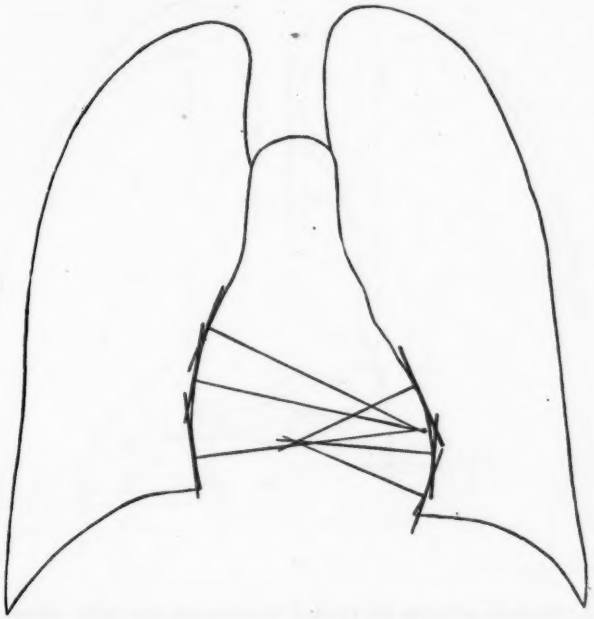

FIG. 6.—Diagram illustrating methods of drawing radii. Three lines are drawn tangent to the curve of the right auricle. At these tangential points perpendiculars are erected. The point of intersection of the perpendiculars is the center of the circle of which the curve is an arc. Each of these perpendiculars present a radius which is measured in centimeters. A similar procedure is followed with the curve of the left ventricle.

scopic devices in which the tube and screen were movable independently of each other, thus making it possible to examine both by the centric and excentric methods. Besides this telefluoroscopic examinations and orthofluoroscopic examinations by a simplified method for the purpose of determining the position of the apex and the points of junction of the chambers were made.

In studying the relationship of cardiac function to habitus, comparative observations were made as accurately as is possible with regard to the following points: First, the rate and regularity per minute of ventricular contraction; secondly, the sequence, force and amplitude roughly of the pulsations of the curves of the right and particularly the left side of the heart. It cannot as yet be stated with any degree of accuracy just what the variation in cardiac function according to habitus is. Perhaps with more thorough investigations with an electrocardiograph or kimoroentgenograph habitus may be found to be associated with certain types of cardiac

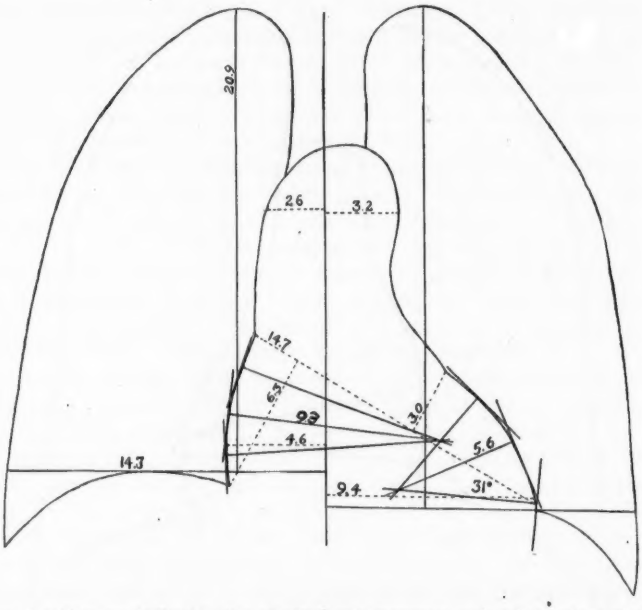

FIG. 7.—Diagram indicating the standard measurements and radial values of the heart of the hyperstenic habitus.

function, especially as regards cardiac muscle tonus, exactly as tone, peristalsis and motility vary in the gastro-intestinal tract according to the habitus.

The actual measurements were made from teleroentgenograms. The technic of teleroentgenography is important not only from the standpoint of individual accuracy but also from the urgent necessity for standardization of this form of radiography, so that the results of all investigators may be truly comparable. The uprights of the tube and screen stands are on scaled tracks, with the upright of the former movable and that of the latter fixed. The screen and tube

are movable in uprights which are correspondingly scaled in one-quarter inch divisions. In this way tube centering, alignment and tube-screen distance are accurately obtained. A target-screen distance of 7 feet 1 inch (85 inches or 215 cm.) is utilized. Schmincke has shown that at this distance the cardiac outline obtained may be regarded as corresponding accurately with the actual anatomical outline. The tube was centered at the level of the sixth thoracic vertebræ. Albers-Schonberg has shown that the greatest transverse diameter of the heart lies in a plane parallel to this level. Bardeen has confirmed this observation on numerous cadavers and on cross-sections of the trunk.

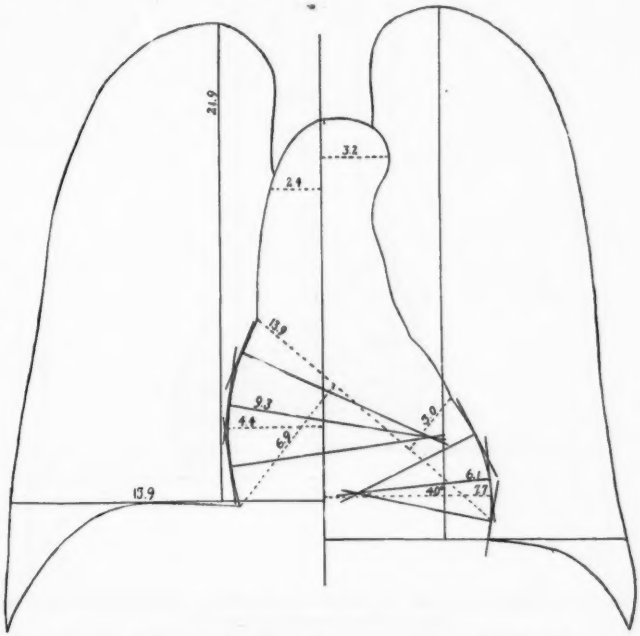

FIG. 8.—Diagram indicating the standard measurements and radial values of the heart of the sthenic habitus.

The exposure was made in the upright position with the anterior chest wall against and parallel to the plate. Depending on the thickness of the chest wall the time of exposure varied from one to three seconds' duration. Exposures were made in full inspiration except in the asthenic type, where they were taken in complete expiration.[4]

[4] The purpose of this procedure is to get the various obliquities of the heart shadows as nearly identical as possible and as small a variation in angle as possible, the averages in our examinations extending from 33 to 48, a variation of but 15 degrees.

Tracings were drawn from the radiographs obtained in this way and the following measurements of the cardiac shadow were made:

1. Transverse diameter—obtained by adding:
   (*a*) Maximum deviation to the right from the midline;
   (*b*) Maximum deviation to the left from the midline.
2. Total length measured from the junction of the right auricle and aorta to the apex.
3. Diameter of the base measured at right angles from the long diameter to the most distant point below on the right and to the junction of the auricle and ventricle above on the left.

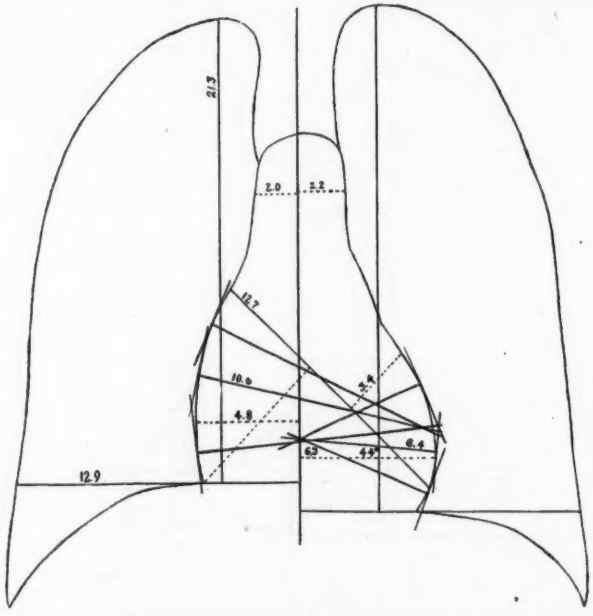

FIG. 9.—Diagram indicating the standard measurements and radial values of the heart of the hyposthenic habitus.

4. The angle formed by the intersection of the transverse and long diameters.
5. Maximum width of the aortic arch at the second rib.
6. Width of the pulmonic fields measured at the level of the diaphragm.
7. Length of the pulmonic fields measured from the apex above to the highest point of the diaphragmatic curve.
8. Radius of the right auricle.
9. Radius of the left ventricle.

Measurements Nos. 1 to 7 inclusive are called the standard

measurements to which it is desired to add measurements Nos. 8 and 9, a measurement hitherto not described. To obtain the radius, for example, of the right auricle three tangents are first drawn to the right auricular curve (Fig. 6). Then perpendiculars drawn from the points where these tangents touch the curve meet at a point which is approximately equidistant to any point on the curve, and a line drawn from this intersection point to any point on the curve constitutes a radius. In a similar manner by drawing

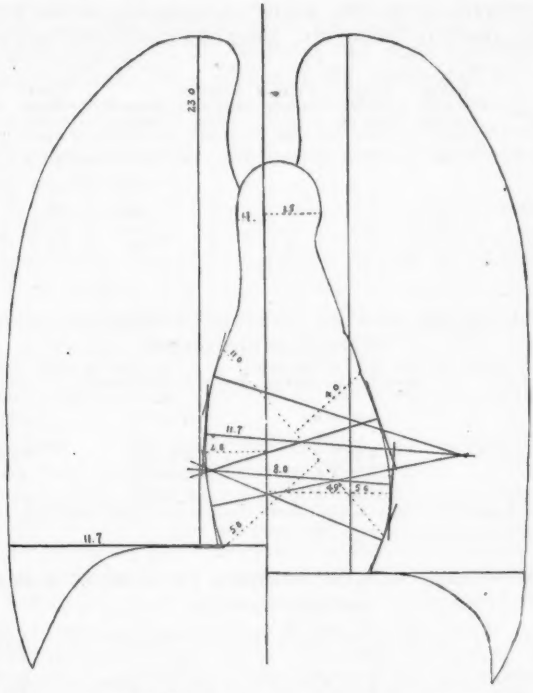

FIG. 10.—Diagram indicating the standard measurements and radial values of the heart of the asthenic habitus.

tangents and perpendiculars to the left ventricular curve its radius may be obtained.[5]

The radius of the curve is utilized as an expression of the size of the chamber.

As yet only the right auricular and left ventricular curves have been studied for the great majority of changes in the normal and

[5] Rarely the lines so drawn do not intersect at a single point. The error is less than three millimeters and negligible.

pathological heart are shown here, and it is the changes in these contours which are the most difficult to read.

It has been found that the radius of the curve varies with the habitus in a certain definite way, and that there is for each habitus a certain definite radius (Table II). When these curves do not conform in their radial value to the habitus the cause of the deviation must be sought for in intra- or extracardiac disease.

TABLE II.—SHOWING RELATION OF RADIUS OF RIGHT AURICLE AND LEFT VENTRICLE TO THE WIDTH AND LENGTH OF THE PULMONIC FIELDS, ANGLE OF OBLIQUITY, CHEST CIRCUMFERENCE AND WEIGHT.

Habitus.	Radius for right auricle, cm.	Radius for left ventricle, cm.	Width of pulmonic field, cm.	Height of pulmonic field, cm.	Angle in degrees.	Chest circumference, cm.	Weight in kg.
Asthenic . .	11.5	8.3	11.6	23.1	48	70.2	45.5
Hyposthenic	10.0	7.7	13.2	23.8	43	78.7	57.8
Sthenic . .	8.9	6.9	14.2	23.0	37	86.9	68.0
Hypersthenic	7.9	6.8	14.4	22.5	33	93.2	72.0

TABLE III.—TABLE SHOWING RELATION OF RADII TO WEIGHT FOR HYPERSTHENIC HABITUS.

Weight in kg.	Radius for right auricle, cm.	Radius for left ventricle, cm.	Angle in degrees.
40 to 50 (rare)	8.5 to 8.0	6.6 to 6.2	30 to 34
51 to 60	8.0 to 7.6	6.2 to 5.9	30 to 34
61 to 70	7.8 to 7.3	6.0 to 5.7	30 to 34
71 to 80	7.6 to 7.0	5.8 to 5.5	30 to 34

NOTE.—A radius for right auricle below 7.0 cm. is considered abnormal. A radius for left ventricle below 5.5 cm. is considered abnormal.

TABLE IV.—TABLE SHOWING RELATION OF RADII TO WEIGHT FOR STHENIC HABITUS.

Weight in kg.	Radius for right auricle, cm.	Radius for left ventricle, cm.	Angle in degrees.
40 to 50	9.5 to 8.8	7.5 to 7.0	35 to 39
51 to 60	9.0 to 8.6	7.2 to 6.8	35 to 39
61 to 70	8.8 to 8.4	7.0 to 6.6	35 to 39
71 to 80	8.6 to 8.0	6.8 to 6.2	35 to 39

NOTE.—A radius for right auricle below 8.0 is considered abnormal. A radius for left ventricle below 6.0 is considered abnormal.

TABLE V.—TABLE SHOWING RELATION TO RADII TO WEIGHT FOR HYPOSTHENIC HABITUS.

Weight in kg.	Radius for right auricle, cm.	Radius for left ventricle, cm.	Angle in degrees.
40 to 50	11.0 to 10.5	8.4 to 8.0	40 to 45
51 to 60	10.5 to 10.0	8.2 to 7.6	40 to 45
61 to 70	10.0 to 9.5	8.0 to 7.4	40 to 45
71 to 80	9.5 to 9.0	7.8 to 7.2	40 to 45

NOTE.—A radius for right auricle below 9.0 cm. is considered abnormal. A radius for left ventricle below 7.0 cm. is considered abnormal.

TABLE VI.—TABLE SHOWING RELATION OF RADII TO WEIGHT FOR ASTHENIC HABITUS.

Weight in kg.	Radius for right auricle, cm.	Radius for left ventricle, cm.	Angle in degrees.
40 to 50	11.7	8.6	46 to 56
51 to 60	11.5	8.4	46 to 56
61 to 70	11.3	8.2	46 to 56
71 to 80 (rare)	11.2	8.0	46 to 56

NOTE.—A radius for right auricle below 11.0 cm. is considered abnormal. A radius for left ventricle below 8.0 cm. is considered abnormal.

The first deviation which occurs in the heart shape as a result of pathological changes in the walls of the heart manifests itself roentgenographically by a change in the contour of the cardiac profile. Such changes cannot be determined by the change in size. Only when well-marked do they produce the characteristic heart shapes, as, for instance, the rounded mitral heart and the oval heart of aortic valvular disease.

The distinct bulging of the pulmonic and auricular curves in well-marked cases of mitral stenosis or patent ductus is sufficiently characteristic to be recognized at a glance, but the beginning enlargement of the auricles as a result of obstruction of the pulmonary circulation, or beginning enlargement in the early stages of valvular disease, or the beginning change in the ventricular walls in arterio-nephritic disease can only be determined by an accurate measurement of the radii of the curves which constitute the profile of the heart shape.

Conclusions. 1. The position of the heart varies with the habitus.

2. The shape of the heart varies with the habitus.

3. That habitus must be taken into consideration in estimating cardiac size.

4. That reasoning by analogy the cardiac function, particularly as regards muscular tonus, may perhaps vary with the habitus.

5. That only by actual measurement of the curves of the heart can the changes in contour be made out in early cases.

6. That the value of the curves varies with the habitus.

7. That the radial value of the curves of the left ventricle and right auricle vary with the habitus.

8. That the radii measurements are a more accurate and valuable expression of impending or established change in the architecture of the heart chambers than the so-called standard measurements.

REVIEWS.

DISEASES OF CHILDREN. By HERMAN B. SHEFFIELD, M.D., formerly Instructor in Diseases of Children, New York Postgraduate Medical School. Pp. 798; 238 illustrations. St. Louis: C. V. Mosby Company, 1921.

THE arrangement of this book is somewhat different from most of the standard works dealing with the subject. There is a division into fourteen chapters which on examination are found to be sections rather than chapters. For example in the first chapter, which is on the Control and Prevention of Disease, the following subheadings are present: Nutrition and Infant-feeding; Hygiene and Sanitation; Immunization; Therapy.

In any book dealing with the period of infancy it is of first interest to turn to the pages on infant-feeding. It is there that the individuality of the author can be discovered. There is not much space devoted to nutrition in Dr. Sheffield's book, but probably as much as the size of the book warrants. After a theoretical discussion of the digestion of protein, carbohydrate and fat, breast-feeding is very briefly considered. It is to be noted here that some pediatrists would take exception to the statement that it may be necessary to remove the baby from the breast because of high fat content in the milk. Such high fat percentage is almost always a temporary matter, and even then rarely disturbs the baby to any great extent. Under artificial feeding of babies it is seen that the author evidently believes in low protein in his mixtures, as all the formulas given are made from top milk when the infant is under three months of age. A rather ingenious arrangement is given for calculating the mixtures required, the calculation being made on age rather than on weight. The necessity for individualization in feeding is recognized. In the tables for feeding older children only the nature of the foods selected is mentioned—the amounts are not stated.

The rest of the book takes up in order the usual diseases of the newborn, the infant and the older child. Subjects of recent interest are given mention, such, for example, as the Schick test, the toxin-antitoxin immunization in diphtheria and the vitamines. Certain lapses are noted in bringing some of the chapters up to date. Thus in spasmophilia the statement is made that it (spasmophilia) is still shrouded in mystery, and no reference is made to the question of a disturbance of the mineral metabolism in its causation.

The illustrations in the book are fair and show a rather large number of unusual conditions. A. G. M.

TRANSACTIONS OF THE AMERICAN UROLOGICAL ASSOCIATION. Vol. XII, 1920. Pp. 353; 83 illustrations. Baltimore: Williams & Wilkins Company, 1921.

THESE *Transactions* contain many valuable and progressive papers. Notable among the thirty-six herein published is Eisendrath's study of "The Relation of Variations in the Renal Vessels to Pyelotomy and Nephrectomy;" Barringer's presentation of "Newer Methods of Radium Treatment of Carcinoma of the Bladder and Prostate;" Smith's "Spinal Anesthesia in Urology."

A. R.

PRINCIPLES OF HYGIENE: A PRACTICAL MANUAL FOR STUDENTS PHYSICIANS AND HEALTH OFFICERS. By D. H. BERGEY, M.D., DR. P.H., Assistant Professor of Hygiene and Bacteriology, University of Pennsylvania. Seventh edition, thoroughly revised. Pp. 556; 63 illustrations. Philadelphia and London: W. B. Saunders Company, 1921.

THIS seventh edition brings Dr. Bergey's well-known manual thoroughly up to date. Into it are incorporated many valuable public-health lessons learned during the World War. The general arrangement and the subjects presented are in the main the same as in the previous editions.

The book has not been prepared merely for medical students and practitioners, but also to aid students in architecture in comprehending the sanitary requirements in ventilation, heating, water-supply and sewage-disposal. Its chief value, however, lies in its simple and accurate presentation of the general principles upon which the health officer and the physician work in their respective capacities in dealing with conditions which are detrimental to health or which tend to improve health. Furthermore, certain chapters, especially those dealing with personal hygiene, food and dieting, exercise and clothing will be of considerable interest and much value to the layman.

It is a pleasure to note that throughout the treatise the metric system of weights and measures is used. This is far simpler than the English system, and although it has been legal in the United States, according to Dr. Bergey, since 1866, it is only now coming into fairly frequent use in the medical profession. Its adoption by such text-books as this will make for its more general use.

In the appendix are included the United States quarantine laws and certain state regulations, and these add considerably to the reference value of the work. On the whole the book deserves the hearty welcome which has been accorded previous editions.

T. G. M.

OPERATIVE SURGERY. By J. SHELTON HORSLEY, M.D., F.A.C.S., Attending Surgeon, St. Elizabeth's Hospital, Richmond, Va. Pp. 721; 613 illustrations. St. Louis: C. V. Mosby Company, 1921.

THE many years' experience of the author has been crystallized in this masterful book on operative surgery. Throughout the text the keynote is the relation of physiology to surgery and the preservation of the functional ability of an organ when its anatomy is necessarily modified by operation. The author lays great stress on a proper conception of the biological phenomena as being of as great importance as the mere knowledge of surgical technic or the ability to perform an anatomically perfect operation.

The volume does not purport to be an encyclopedia of all surgical procedures, but is a selection of those personally found to be of the greatest value, although in many instances several operations appropriate for different aspects of the same underlying affection will be found. Especially, in view of their excellence, mention must be made of the chapters on plastic surgery and the surgery of the bloodvessel system, in which the author is a recognized master and authority. Systemic surgery is described in the various chapters in a style easily readable, with the description clear and quickly comprehensible and with sufficient discussion of the variations of conditions and complications to be met. In addition to the chapters on systemic surgery there are sections dealing with technic, complications, drainage, transfusion, incisions and the general principles of operative surgery. The book is splendidly and profusely illustrated. The volume will take its place at once in the front rank of the text-books on operative surgery. P. F. W.

DISEASES OF THE SKIN. By J. M. H. MACLEOD, M.D., Physician for Diseases of the Skin, Charing Cross Hospital; Physician for Diseases of the Skin, London Hospital for Tropical Diseases; Physician to the Skin Department, Victoria Hospital for Children; Lecturer on Dermatology, Charing Cross Medical College and London School of Tropical Medicine; formerly editor of the *British Journal of Dermatology;* Vice-President, Dermatological Section of the Royal Society of Medicine; Membre de la Société Française de Dermatologie; Corresponding Member of the American Dermatological Association. Pp. 1307; 23 illustrations in color and 435 figures in black and white. New York: Paul B. Hoeber, 1921.

MACLEOD, after a thorough and complete understanding of the normal histology and pathological changes that occur in the skin,

has completed an excellent text-book on dermatology. It is unusual for one author to have written extensively in book form on the pathology of the skin, and in addition a text-book on dermatology covering all phases of this important subject.

MacLeod's work both as to illustration and text is monumental, as very few books on dermatology have attained this proportion and completeness.

The preliminary portion of the subject is unusually well covered—158 pages of text help the reader in the elucidation of the individual diseases. Classification of the various diseases has again, as in other text-books on the subject, proved difficult, as the etiology of so many dermatological conditions is as yet unfathomed.

The diseases of the skin are described under the following headings: Congenital affections of the skin; cutaneous affections due to cold; cutaneous affections due to heat; cutaneous affections due to sunlight; dermatitis due to electricity, roentgen rays and radium; dermatitis due to local irritants; cutaneous affections due to streptococci, to staphylococci, to fungi, to bacilli, to protozoa (syphilis), to animal parasites; pruritus; erythemata; urticaria and allied conditions; drug eruptions; lichen; eczema and rosacea; scaly affections; vesicular and bullous affections; lupus erythematosus; mycosis fungoides; affections of the cutaneous bloodvessels; anomalies of pigmentation; atrophies of the skin; affections of the hair, of the hair follicles, of the sebaceous glands, of the sweat apparatus, of the nails, of the lips and mouth; benign neoplasms of the skin; malignant neoplasms of the skin; pseudoneoplasms of the skin and tropical affections of the skin.

The photographs are excellent, the illustrations in color good, but some are of a rather vivid hue.

The volume is a credit to the author and the publisher, and can be thoroughly recommended as one of the best works on dermatology extant. F. C. K.

THE TREATMENT OF ACUTE INFECTIOUS DISEASES. By FRANK SHERMAN MEARA, M.D., PH.D., Professor of Clinical Medicine, Cornell University Medical College; Consulting Physician to Bellevue Hospital, New York; to the Mountainside Hospital, Montclair, N. J.; to the Morristown Memorial Hospital, Morristown, N. J., etc. Second edition, revised. Pp. 806. New York: The Macmillan Company, 1921.

A REVISION of the original text has been made to accommodate the many changes necessitated by the increase in the knowledge of certain of the acute infectious diseases, such as measles, streptococcus pneumonia and meningitis. The results of epidemics in the military camps have added to the literature much information of value.

The author has added in addition descriptions of the more common acute infections of the upper respiratory tract, such as coryza, tonsillitis, laryngitis and tracheobronchitis and a chapter on acute pleurisy. Encephalitis lethargica and trench fever have been added and rat-bite fever and Rocky Mountain spotted fever have been revised. It was thought advisable to retain the chapter on grip, although a new chapter was devoted to epidemic influenza. The book is well written, well arranged and convenient for reference. The references to the literature are given in footnotes on each page as they occur. There are at times direct quotations of the original reference. A complete, systematic summary is added to each chapter. Containing as it does the essence of the text set forth in the briefest form, but still containing the most important points of information, the book becomes an invaluable, handy reference for the busy practitioner, while the completeness of the text renders it an important addition to the library as a source of more detailed and recent information. The reproduction of many prescriptions and the descriptions of non-medicinal methods contribute to its value as a therapeutic guide. A. E. S.

GEORGE MILLER STERNBERG: A BIOGRAPHY. By his Wife, MARTHA L. STERNBERG. Pp. 331. American Medical Association, 1920.

THE American Medical Association is to be congratulated in a departure from policy when it published Sternberg's *Biography*. In this volume is reviewed, by his widow, the life of a man who helped in a large measure to make American medicine and its history. The story is intensely interesting, because Dr. Sternberg's career was full of hard work and achievement. Mrs. Sternberg tells entertainingly of his days spent at military posts combating cholera and yellow fever; of his pioneer bacteriological work, and of his activities as Surgeon-General during the Spanish-American War. The conquest of yellow fever is one of the great episodes in medicine. Three names are suggested in this connection: Sternberg, Reed and Gorgas. It is fortunate to have such an excellent biography of the first member of this illustrous trio. T. G. S.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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Manipulation of Stiff Joints.—JONES (*Jour. Orthop. Surg.*, 1921, iii, 385) says that one of the difficult problems presented to a surgeon is the decision as to when a stiff joint is to be moved and when it is to be rested. A painful joint which is rigid in all directions is the seat of an arthritis, while a painful joint which is rigid in certain directions only, movement being normal in others, is free from arthritis but subject to adhesions. Adhesions may be divided into two groups—intra-articular and extra-articular. Adhesions are avoided by the early and safe resort to active and passive movements. These movements should be practically painless and should consist mainly in assisting the patient to move his own joints. Light adhesions may be broken down under gas; if strong and resistant, full anaesthesia is best. The joints should be moved through the full anatomical range unless adhesions are very firm. The pump-handle method as applied to the breaking of adhesions or the practice of passive movements is to be avoided. Voluntary efforts, however, can be repeated with advantage as often as the patient can be persuaded to make them. If effusion should take place in a joint after manipulation, it is strongly suggestive of the rupture of intra-articular adhesions. If the range of movement is diminished by use and exercise the joint requires rest. If even in the presence of pain the range of movement is increased by exercise, rest is contraindicated.

Some Aspects of the Mechanism of the Human Foot in Walking.—GIBSON (*Jour. Orthop. Surg.*, 1921, iii, 158) says that the foot is essentially a kinetic mechanism and that the term "arches" applied to the various parts of it is not so accurate nor so significant as the term "springs." Without entering deeply into the mechanics of springs it is evident that the more flexible the material the greater will be the power of the spring to convert a vertical impulse into a horizontal deformation—the larger it is the greater the amount of such conversion. One other quality is a prime necessity in a spring, namely, strength.

In the human foot there are two springs but not with independent action. The outer spring is made up of the following bones: os calcis, cuboid, fourth and fifth metatarsals. The inner spring is made up of the os calcis, scaphoid, the three cuneiforms and the first three metatarsals, especially the first. In both cases the point of maximum convexity of the spring is supported by a tendinous sling whose upper attachment is to the bones of the leg. The peroneus longus is on the outer side, the tibialis posticus on the inner side.

Fractures of the Elbow in Children.—STONE (*Jour. Orthop. Surg.*, 1921, iii, 395) says that reduction should be attempted with the elbow fully extended if necessary. The elbow is then held flexed midway between pronation and supination by strapping the wrist to the shoulder with adhesive plaster and adding the support of a sling. The flexed position should be maintained for two weeks. Then a change to a right-angled splint for at least three weeks then, finally, a sling for a week as a safeguard against accident before natural use in play. Passive movement is either useless or harmful, or not only the synovial cartilage but the large masses of epiphyseal cartilage tend to prevent rought jagged ends from traumatizing the delicate synovial membrane. The two causes of limitation of motion after elbow fracture in children are spasm and deformity. Spasm indicates one thing, that motion would cause pain—nature demands rest till spasm is gone. In deformity the limitation is clean-cut—definite, comparable to the stopping of a door by an obstruction. Primarily the deformity is bony, in part the result of imperfect reposition of the fragments, in part of callus formation. Secondarily there may be all sorts of ligamentous and muscular readjustments which limit motion. In overcoming deformity the decrease in the size of the callus, the gradual absorption of bony projections and adaptive changes are the essential factors. One group of cases requires open reduction, namely, those in which the epiphysis of the external condyle has been detached and has turned turtle. The slightly concave fractured surface points upward, outward and backward. The articular surface lies in contact with the fracture line at the lower end of the shaft. In epiphyseal separations about the elbow joint the rœntgen-ray may often be wholly negative. The diagnosis must be made by history, the disturbed function and local tenderness. Volkmann's ischemic contracture is one of the most serious and distressing complications of elbow fractures. Any muscle deprived of its blood supply for a period of six hours undergoes degenerative changes from complicated muscle cell to low-grade scar tissue. Contraction of the scar causes flexion of the muscles.

Reconstructive Surgery of Traumatic Foot and Ankle Deformities.—COTTON (*Jour. Orthop. Surg.*, 1921, iii, 196) says that the functions of the foot in order of their importance are to support the body weight, to give attachment to the muscles of the legs and foot, to act as a lever in progression, to furnish the spring movements in walking by permitting lateral and up-and-down movements. Traumatic deformities of the foot and ankle which interfere with the normal function may be caused by injury or infection of the bones of the leg or ankle joint, bones and joints of the tarsus; injury or infection of the muscles or tendons, injury to nerves supplying motor function to muscles of the leg and foot. The

most common cause of traumatic weak foot is unreduced Pott's fracture —the most common variety is fracture of the fibula about three inches above the external malleolus. This type when unreduced gives us the typical traumatic flat foot. It is necessary to restore the alignment of the foot to the leg, to put the foot back in gear with the leg. This can be brought about by osteotomy of the tibia and fibula above the old fracture or by refracturing the bones at the site of the old fracture. Another type of deformity is due to unreduced fracture of the lower end of the tibia extending into the ankle joint an acquired talipes equino-varus. The simplest method of treatment is by tenotomy of the tendo Achillis and other resisting tendons or fascia and wrenching, combined with osteotomy of the tibia and fibula above the ankle joint. Another common cause of deformity and prolonged disability of the foot is fracture of the os calcis. The lateral deformity of the fracture with the shortening of the tissues on the outer side of the ankle and of the peroneal tendons furnishes the pathology for the clinical condition of rigid weak foot. The prophylactic treatment is the reduction of the fractured os calcis by manipulation with furnishing of proper support to the foot when weight-bearing is begun. When the condition has developed the treatment is practically the same as that of rigid weak foot. The principles used in the treatment of osteomyelitis with deformity are, first, the thorough operative removal of the diseased bone by the cone method with correction of the deformity by osteotomy, followed by frequent cleansing of the wound and prevention of pocketing. The weight-bearing function is the first object of all treatment. Unnecessary risks and fanciful operations should be tabooed.

Non-operative Treatment of Scoliosis.—TRASLOW (*Jour. Orthop. Surg.*, 1921, iii, 228) says that successful treatment of structural scoliosis must depend upon a clear understanding of the elements of deformity and the lessening, if not complete elimination, of all of them. Uniform and regular measurement and numerical record of the elements of deformity are important as guides to continuance of treatment and as indicating elements most needing correction. A balanced use of corrective plaster-of-Paris jackets, of retention braces and of internal exercises is essential in satisfactory results. The position of the patient when the plaster jacket is applied is responsible for improving body posture and shoulder carriage; the successive paddings are for care of the spinal deviation and rotation. The essentials of a retention brace are ability to hold correction attained, application by the patient with reasonable accuracy, extensibility and lateral compressibility to meet normal growth and progressive deformity decrease; mechanical self-correction by the brace seems possible but not yet fully attained. Gymnastic exercises must be progressive, intensive and with a minimum of erect weight-bearing. They must aim to correct all of the elements of deformity, especially that of rotation. Starting positions other than standing facilitate these ends. Retention of deformity correction attained must be maintained while exercise is developing natural muscular support. Artificial support may gradually give way to natural support. The paralytic scoliotic must receive a larger proportion of artificial support than will be required for those not paralyzed in trunk muscles. Internal splinting by operative bone fixation may also be necessary in severe paralytic cases.

THERAPEUTICS

UNDER THE CHARGE OF

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Etiology of an Outbreak of Infectious Diarrhea.—WEISS (*Arch. Int. Med.*, 1921, xxviii, 37) states that out of 422 cases of diarrhea occurring in the autumn of 1918 in the A. E. F. at the St. Anne Barracks, Nantes, only 15 required hospital care. Eight of these were available for study and from 7 a Gram-positive micrococcus was isolated from one or more sources—in 4 cases from the feces, in 6 cases from the urine and in 1 case from the blood. The eighth case, the only negative one, was convalescent. The author describes the organism carefully and shows the identical manner in which the various strains react on fermentation mediums and with serum agglutination tests. He was able, also, to produce diarrhea in Macacus rhesus monkeys by feeding them the organism, and in a number of these cases the disease proved fatal and the organism was recovered at postmortem. A monkey actively immunized by a polyvalent vaccine made from these cultures was subsequently resistant to infection. The author concludes that the evidence presented suggests the etiological relationship of the organism described to infectious diarrhea in the outbreak studied.

Modern Methods in Handling Hospital Statistics.—PEARL (*Bull. Johns Hopkins Hosp.*, 1921, xxxii, 184) shows the value of and need for careful statistical investigation of medical data in a modern hospital. He gives the functions of a statistical department: (*a*) Assembling and tabulating routine statistical data; (*b*) organization of special department records; (*c*) consultant service (of expert statistician to persons publishing papers); (*d*) research (special biometrical investigations). He discusses the hospital records and points out the commonest defects: "The advantages of this method of preserving histories (the so-called 'unit system' of case histories) over the far more common system of binding them in great volumes in numerical or temporal sequence are so obvious as not to need detailed exposition. Such a method is really essential." The modern system of mechanical tabulating and indexing is described whereby records are transferred, by means of a machine called a "key punch," to cards, the record on the card appearing as a series of punch holes. Then by means of another machine, known as a "sorter," the punched cards can be mechanically sorted at a rate of 250 cards per minute into any desired arrangement. The pertinent cards thus sorted need only be run again through another machine, known as a "tabulator" and the results relative to any desired category of information will be mechanically

counted and tabulated. The organization of the card forms is shown and fac-similes are produced of (*a*) the primary card, (*b*) the secondary card, and of (*c*) five special cards (now in use in the Brady Urological Clinic of the Johns Hopkins Hospital). The statistical department in a modern hospital should consist of a chief statistician, an assistant statistician and four clerks. He details the material equipment needed.

The Intravenous Administration of Calcium Acetyl Salicylate.—CAMPBELL (*British Med. Jour.*, July 9, 1921, p. 37) states that acetyl salicylic acid is in part decomposed into salicylic acid and absorbed as salicylate—that part is taken into the blood stream unchanged. The salicylate formed from it exercises its usual antipyretic action on the tissues. The undecomposed molecule is responsible for the analgesic action in headache, neuralgia, etc. It occurred to Campbell that the analgesic action could be greatly increased if the drug were injected directly into the blood stream, thus avoiding decomposition in the alimentary tract. Since acetyl salicylic acid is only slightly soluble, calcium acetyl salicylate was used. The results more than fulfilled expectations; the pain is relieved in one-half to three-quarters of an hour and the effect persists for several hours and in some cases for days. Among the painful conditions that yielded to this new therapy were sciatica, acute rheumatism, tabes dorsalis, interstitial keratitis, acute iritis, arsenical neuritis, dysmenorrhea, etc. It is noteworthy that one patient who was unable to take sodium salicylate or acetyl salicylic acid by mouth was promptly relieved by calcium acetyl salicylate by vein.

The Salicylates. XIII. The Liberation of Free Salicylic Acid from Salicylate in the Circulation.—It has been claimed that the absence of a right-sided valvular endocarditis is due to the antiseptic qualities of free salicylic acid liberated in the right heart by virtue of the greater carbon dioxide content of the venous blood; that the occurrence of initial endocarditis is associated with the greater alkalinity of the arterial blood, which cannot liberate free salicylic acid and consequently does not possess antiseptic qualities. Although HANZLIK (*Jour. Pharm. Exp. Therap.*, 1921, xvii, 385) admits that this view is not compatible with the modern conceptions of the mechanism of neutrality regulation of the blood, he thought it desirable to put it to a test. Animals were injected with salicylate and were subjected to the most favorable conditions for reduction of the alkalinity of the blood, mainly by means of fatal asphyxia. But first it was necessary to determine the degree of acidity necessary for the liberation of free salicylic acid from salicylate *in vitro*. It was found that free salicylic acid is demonstrably liberated from the sodium salt at a low degree of acidity, one whose hydrogen-ion concentration corresponds to pH=6.7; more definitely at pH=6.5. The presence of 25 per cent serum or plasma in salicylate "buffer" mixtures prevents the liberation of free salicylic acid at the high degree of acidity of pH=5.9. Therefore it is improbable that free salicylic acid could be demonstrated in the circulation during life. This was fully confirmed on animals subjected to fatal asphyxia whose cardiac and arterial bloods were rendered very slightly acid (pH=6.8 or 6.9). Consequently the theory that free

salicylic acid liberated by virtue of the greater CO_2 content of the venous blood of the right heart exerts an antiseptic action and prevents the development of a right-sided auriculoventricular (tricuspid) endocarditis in rheumatic fever is untenable. An explanation of the phenomenon must be sought elsewhere.

The Action of Drugs in Infection.—I. The Influence of Morphin in Experimental Septicemia.—KRAFT and LEITCH, (*Jour. Pharm. Exp. Therap.*, 1921, xvii, 377) report that morphin lowers the resistance of rabbits toward septicemia produced by Streptococcus hemolyticus. Just how this decreased resistance is brought about they fail to determine, but suggest that the harmful influence of morphin is due to several factors: Inhibition of phagocytosis, increase in intestinal stasis and a depression of body temperature, of metabolism and of the body defence. While there can be no doubt of the value of the sedative action of morphin in certain non-inflammatory conditions the authors are convinced that opium and its derivatives must be prescribed with great caution to those patients who are suffering from diseases associated with inflammation.

PEDIATRICS

UNDER THE CHARGE OF

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Feeble-mindedness in Hereditary Neurosyphilis.—RAEDER (*Am. Jour. Dis. Children*, March, 1921) studied thirty children ranging in age from two to sixteen years. In either one or both parents there was a positive Wassermann reaction on the blood serum. Most of the parents had neurosyphilis usually of the paretic type. Either blood serum or blood serum and spinal fluid Wassermanns were made, in all thirty cases. Of these nineteen showed a definitely positive Wassermann reaction. With few exceptions the older children or those born nearest the time of the parental infection showed a positive Wassermann, while the younger and farthest removed showed a negative Wassermann. On twenty-two of the thirty children spinal fluid was obtained and in four of these a positive Wassermann reaction was returned. Psychometric examination of these children showed psychic steps corresponding to the grades of physical defects. Mental deficiency in congenitally syphilitic children of not feeble-minded parents is usually due to syphilis.

The Electrocardiogram in Normal Children.—SEHAM (*Am. Jour. Dis. Children*, March, 1921) found that in the premature in the first three months of life the normal electrocardiogram indicates that there is a right ventricular preponderance. At about the fourth month the $R1$ becomes longer than the $S1$, and from then on the ventricular com-

plex approaches the adult type of curve. In general the average height of deflections in children are greater than in the adult. Except in the premature satisfactory records showing all the deflections seen in the normal adult electrocardiogram can be obtained during any period of childhood. The *P* is higher in childhood than in the adult in all three leads except in the premature. It was absent in only two cases of this series. It was found electronegative in eight records. The *Q* plays a prominent part in the electrocardiogram of childhood. It is larger in Leads II and III. Altogether it adds confirmatory evidence that there is a right ventricular preponderance in the first few months of life. The *R* in Lead I during the first few months of life is lower than at any other period, but in Leads II and III it averages higher than in the adult. The increase of *R*1 corresponding with the decrease of *S* in Lead I is also an indication of a right ventricular preponderance during the earliest periods of life. The *S* deflection is the most characteristic and distinctive of the ventricular complex in childhood. In Lead I it is both relatively and absolutely higher in the first three months than in any other period of life and in the other leads it is relatively higher than in the adult. The *T* is very susceptible to external influences in the child and therefore its height is unreliable. In the first ten days it is quite frequently absent. After that it is quite constant. It was found inverted but only during the latter part of childhood in 15 per cent of the readings. The general impression that the younger the child the more frequent the arrhythmias was not confirmed by the electrocardiograph. The younger the child the faster the pulse and the faster the pulse the less frequent the arrhythmia. In the newborn the average difference between the highest and the lowest pulse periods was $\frac{2}{5}\frac{}{0}$ second. Whereas in the older children from six to thirteen years of age the average difference was 4 $\frac{3}{5}\frac{}{0}$ seconds. In the period of infancy no sinus arrhythmia occurred, while in the school age 47 per cent showed it. The transmission time in children is, on the whole, of shorter duration than in the adult. In the newborn the auricular activity occupies an average of 0.18 second, whereas in the last period of childhood it consumes an average of 0.19 second. In the adult the *R* interval averages 0.18 second. In the newborn it averages 0.21 second and gradually increases until at the school age it averages 0.34 second. In the adult the average for *RT* phase is 0.36 second.

Safety-pins in the Stomach.—JACKSON and SPENCER (*Jour. Am. Med. Assn.*, February 26, 1921) report two cases in which the pins were removed by mouth without anesthesia. Discussing foreign bodies in the alimentary canal they say that in most cases foreign bodies that have reached the stomach without having been pushed down will pass harmlessly through the intestinal tract. Enough exceptions arise that make it necessary to watch the foreign body at frequent intervals by fluoroscopy until the foreign body is passed. During this time no change should be made in the diet and laxatives are not to be given. Open safety-pins have been passed by rectum, but removal from the stomach by mouth is advisable where the pin is so large relatively to the size of the patient that there is some doubt that it will pass, and also when waiting for from three to eight weeks has demonstrated that the pin will probably not pass. There is little likelihood that a foreign body

will be regurgitated. The safest and best method is by peroral gastroscopy. When a skilled endoscopist is not available external operation by a skilled surgeon is safer and more successful. When a number of bodies is in the stomach, as frequently happens in the insane, external operation is the best procedure.

Physical Defects in Children.—EMERSON (*Am. Jour. Dis. Children*, March, 1921) examined 607 children. He found that children reported to be sufficiently well to attend school and to engage in the activities of normal children were found to average 5.2 physical defects of all kinds and 2.5 of nasopharyngeal defects. Children brought to a hospital clinic for examination and treatment showed an average of 6.8 general defects and 3.5 nasopharyngeal defects. The distribution of defects according to age was remarkably uniform. In each group studied the largest number of children were between the ages of seven and nine years. These years showed the greatest average number of defects in the Massachusetts General Hospital group as 7.2, but in the Little Wanderers' Home group the highest average number of defects, 6.0, was found from ten to twelve years. Only nine children in the 602 were free from defects. The nasopharyngeal defects appeared in a large number of cases and also totaled a greater number of defects than any other group.

Stigmata of Predisposition to Bone and Joint Tubercle.—RIVERS (*British Jour. Dis. Children*, October to December, 1920) says that denial or neglect of intrinsic predisposition to bone and joint tubercle betokens not only the lack of clinical insight but an unfamiliarity with the literature. It would seem that a part of such a predisposition is not due to a single undefined susceptibility but was multiform and made up of several abnormalities acting probably by mechanical facilitation of infection or else associated with other undiscovered abnormalities acting in a like manner. For the facts and findings concerning pigmentation, ichthyosis, nasal defect and mental unsoundness they are best explained in the light of intrinsic contributory causes. There are obviously several practical bearings, diagnostic, prophylactic and others. There is also a eugenic aspect which is rather important. The author feels that no tuberculous ichthyotic, unless of great intellectual attainments, and no tuberculous mental defective, should be allowed to reproduce.

Roentgen-ray and Tuberculosis in Infants and Children.—O'BRIEN and AMES (*Jour. Am. Med. Assn.*, May 28, 1921) studied forty-four infants and children. They found that the von Pirquet and intracutaneous skin reactions were reliable tests of infection with the tubercle bacillus and the number of positive reactions increases from infancy up to childhood, all their patients over ten years of age reacting. In twenty-six of thirty-six positive skin reactions the roentgen-ray disclosed the site of infection to be intrathoracic. D'Espine's sign as a clinical index of tuberculosis of the bronchial lymph glands is of relative value, being elicited only eleven times as against roentgen-ray evidence of tuberculosis in twenty-eight cases. Three cases of positive sputum were found in fourteen diagnoses of chronic pulmonary tubercu-

losis. Fourteen cases of chronic pulmonary tuberculosis of the adult type were found. Fifteen cases that were negative clinically showed definite roentgen-ray evidence of structural changes of tuberculous infection. This raises the question as to whether these children are not liable to develop clinical tuberculosis, and they should be watched carefully and roentgen-rayed frequently.

Exercise Tolerance of Children with Heart Disease as Determined by Standardized Test Exercises.—WILSON (*Jour. Am. Med. Assn.*, June 11, 1921) found that the circulatory reactions after test exercises in 45 normal children and in 116 children with heart disease confirmed the results of the study of a previously reported group of 20 normal children. A working table was formulated of standardized test exercises followed by normal systolic blood-pressure curves without symptoms of dyspnea and fatigue. It was standardized from an analysis of the reactions of an average group of 65 normal children according to age, weight and height. The degree of distress and type of systolic blood-pressure curve following the standardized test exercises was used as a gauge in estimating the exercise tolerance of children with heart disease. Of the 71 children having definite organic heart disease without symptoms of insufficiency, 69 per cent had a normal tolerance for standardized test exercises, 29 per cent had fair tolerance and 2 per cent had a poor tolerance. In children with chronic organic heart disease, exercise tolerance tests give important and useful information which may be utilized as a scientific basis for intelligent regulation of the child's activities. The observations resulting from this investigation would seem to indicate that the fear of exercise is unwarranted and that a wider latitude may be permitted with safety.

OBSTETRICS

UNDER THE CHARGE OF

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Pregnancy Complicated by Pyelitis.—BAUGHMAN (*Am. Jour. Obst.*, February, 1921, p. 436) reports three cases of pregnancy complicated by pyelitis. These patients were under observation for a considerable time, were treated by lavage of the pelvis of the kidney and pyelograms were taken from time to time as the pelvic size changed. They were private patients treated in a private hospital. The first was a multipara who, during her second pregnancy, had slight nausea at first, which later became severe, with persistent vomiting. There was pain over the abdomen and back, with the greatest tenderness over the right kidney. There was no elevation of temperature and the urine obtained by the catheter was acid, with a few pus cells. The Bacillus coli communis was found on examining the urinary tract, and the patient was treated by irrigation of the pelvis of the kidney. This was followed by increased appetite and improved general condition, and at the fifth irrigation a pyelogram of the kidney was taken. This showed great

distention of the right kidney, pelvis and ureter; moderate distention of the left pelvis and ureter. Both ureters were kinked and tortuous. At the sixth irrigation the patient suffered considerably; her appetite was impaired and she was nauseated. Labor was accordingly induced, and after the birth of the child five irrigations were given, the first fourteen days after delivery. The patient passed through an attack of cystitis, which was treated by daily irrigation of the bladder, followed by instillations of mercurochrome. The patient ultimately made a complete and satisfactory recovery. The second case was that of a primipara who had severe pain in the back and right side and a temperature as high as 104° F. There was frequent urination followed by burning sensation. Three chills occurred in one day. The leukocytes were 16,000; the urine was acid, with a trace of albumin and some pus cells. During the acute attack the patient suffered from nausea. After three irrigations of the bladder the patient seemed better, but after the fourth there was much nausea for two days. The fifth irrigation was given with mercurochrome, which seemed very little irritating, and it was then possible to make a picture of the kidneys. This showed the left pelvis and ureter moderately distended, the right pelvis and ureter more dilated than the left, the kink in the ureter below the pelvis, but below that point there was dilatation. The vertebral column of the fetus was shown in such a position as probably to interfere with the emptying of the pelvis of the kidney on that side. The patient seemed to improve until the ninth irrigation, when it was found that the pelvis of the right kidney was not draining. A pyelogram taken showed moderate dilatation of both kidney pelves, especially marked on the right side. The ureters in the upper part were distorted. After the twelfth irrigation, of 2 per cent. of nitrate of silver solution, against the advice of the physician the patient went home immediately after the irrigation. She suffered considerable pain and had a restless night. Labor began, the child was born asphyxiated, was resuscitated with difficulty, but died a few hours later. Eleven days after delivery irrigation was again resumed with a fairly good result. A pyelogram showed ureters normal, the left pelvis in good condition, the right pelvis of the kidney only partially filled, with accumulation of solution in the calyces. It was thought that possibly the right kidney was smaller than the left. The patient's general condition was good. His third case was that of a multipara who suffered from severe nausea and vomiting for a period of ten days. There was pain in the back and abdomen and great tenderness over both kidneys, especially the right. The urine was acid, with pus and red blood cells; there was moderate elevation of temperature and mucus in the discharges from the bowel. On examination the blood leukocytes were 8000. The patient was considerably improved by three irrigations, when she began to have attacks of sweating. After the fifth irrigation it was possible to take a pyelogram, when the right pelvis and ureter were found greatly distended. The left was normal. The patient was treated with several irrigations, which seemed to produce benefit. Following the taking of a pyelogram, vomiting, headache and nausea returned to a considerable extent and the catheter was left in the pelvis of the right kidney for two hours after one of the irrigations. The patient seemed better for the treatment, and as the child was viable and the pelvis of the left kidney showed signs of becoming involved, labor was induced. The birth of the child was normal and fourteen days

after delivery the mother again received irrigation, and a pyelogram was made. There had been some improvement in the condition of the pelvis of the right kidney, and there was a kink in the right ureter near the pelvis. The patient finally went to her home and another examination made later showed a slow but definite improvement. Repeated examinations during the next few weeks showed that the patient's condition had reached a point where it was almost normal. These cases illustrated the fact that the pelvis of the right kidney is more often involved. In two of these patients the bladder was very constantly involved; in one case inflammation of the bladder was occasionally present. In two of the cases the colon bacillus was the exciting cause and in one the Staphylococcus albus. The pelves of the kidneys were almost of the same size as regards right and left. Irrigation seemed uniformly useful. Apparently the ureters had been obstructed by the pressure of the pregnant uterus because there was marked improvement after delivery. It was interesting to observe that the right kidney in one case was congenitally small and that there was a compensatory increase in the function of the other kidney. In the puerperal period irrigation was well borne as early as two weeks after the birth of the child. Fever was absent with these patients, which seemed unusual in view of the severity of some of the symptoms. Apparently the pelvis of the kidney may become greatly distended and yet resume its normal condition. In one case 100 cc of urine were obtained from the pelvis of one kidney. It is interesting to note that when labor was induced at a selected time, when the condition of the mother was good, that the children were born living. When labor developed without induction the child was stillborn. In discussion it was stated that, owing to the mechanical conditions in pregnancy, there was frequently stasis, followed by lowered resistance, migration of bacteria and infection of the kidney. The last usually comes directly from the colon and the bacteria found are colon bacilli. A mixed infection sometimes occurs. When the colon bacillus and staphylococci are both present there is more resistance to treatment. Good results have been obtained by the introduction of the ureteral catheter, leaving it twelve hours at a time. This apparently gives better results than irrigation, as irrigation seems to increase the dilatation of the damaged kidney. It is valuable to vary the position of the patient in treating and studying these cases. After recovery has apparently occurred, if the patient has slight disturbance in the functions of the kidneys and bladder bacteria will often be found in the urine. An important cause in the development of infection of the urinary tract is retention of urine in the bladder, and in these cases care must be taken to avoid that. In local treatment nitrate of silver is especially valuable, following thorough irrigation with boric acid to clear away the urine. If this is not done the silver will not be precipitated by the chlorides. In these cases the ureters, where they go into the bladder, are intensely congested, and this is also true to a lesser extent throughout their entire course. Nitrate of silver is not only a good antiseptic but a valuable astringent. After a severe labor cystitis and infection of the kidney may develop, because of mechanical injury during labor. Retention of urine and bad drainage from the kidney are usually the important factors in such a case. These patients often improve very slowly, and it may be necessary to carry out treatment energetically and for some time.

The Mortality of Parturition.—Davis (*Jour. Am. Med. Assn.*, February 21, 1920, p. 523) contributes a paper upon this subject. Much of his data is obtained from applications for insurance in life insurance companies. He draws attention to the lack of suitable hospital accommodations for parturient women. He considers the midwife a menace and believes that obstetric surgery and practice should be done in the homes of patients only under the most favorable conditions. Mortality statistics show that for women of the child-bearing age, fifteen to forty-five, childbirth is the second greatest cause of death. Life insurance records show that, for all women insured under forty-five years of age, the diseases of pregnancy and of the puerperal state constitute the second greatest cause of death. Nephritis and so-called Bright's disease and childbirth occupy the fifth place as to causes of death among insured women. A study of 10,000 family histories given by applicants for insurance shows that 1 in every 17.3 associates the death of a mother or sister or both with childbirth, 1 in 28.3 with tuberculosis, 1 in 45 with cancer. It is known that a considerable percentage of these deaths are inaccurately recollected, hence these records are often not accurate in showing the frequency with which childbirth is the contributary cause of death.

GYNECOLOGY

UNDER THE CHARGE OF

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New Uterine Suspension Operation.—A review of gynecological literature for any given year would not be complete if mention were not made of at least one of the dozen or so new operations for suspension of the uterus which are thrust upon the profession every year. One of these new operations has been described by Grad (*Am. Jour. Obst., and Gynec.*, 1921, I, 411), and consists essentially of a subperitoneal shortening of the round ligaments. He has performed several hundred of these operations during a period of eight years, and from a review of one hundred cases in which a follow-up study was made, he is convinced that his operation eclipses all its predecessors. Such a feeling, however, is rather common among inventors of operations. In brief, the technic of the operation consists of grasping the round ligament midway between its cornual insertion and the internal ring and putting the ligament on tension. Immediately below the grasp of the forceps the operator picks up the anterior layer of the broad ligament with a thumb forceps and nips it with a scissors. Beginning at this point, with the scissors, the incision in the anterior layer of the broad ligament is extended along the edge of the round ligament, until the internal

ring of the inguinal canal is reached. In this manner the entire round ligament is divested of its peritoneum and the broad ligaments are separated. A stitch of linen is then taken in the pillars of the ring, which also picks up half of the round ligament as it enters the ring, and then with the same suture the round ligament is picked up, inside of its denuded area, about one inch from its uterine end and the two points of the ligament are brought together by tying the suture. The uterine end of the ligament is then sutured to the pillars of the internal ring with a few linen sutures and the intervening redundant portion of the round ligament is sutured together and then buried between the layers of the broad ligament, all of this being accomplished with the original suture. The anterior layer of the broad ligament is then sutured with catgut to the posterior surface of the round ligament, burying the redundant round ligament and covering all raw surfaces. After the procedure is performed on both sides the operation is frequently supplemented by shortening the uterosacral ligaments or by a ventrosuspension by means of a single catgut stitch, so as to be only temporary in nature. As a result of the author's investigation into this subject he concludes that every case of retroversion of the uterus with symptoms requires an abdominal section, and for this purpose the above operation is readily performed and is not time-consuming, creates no abnormal conditions in the pelvis, tunnels no holes through the abdominal parietes, causes no intraperitoneal complications, does not interfere with pregnancy or labor, is devoid of mortality and morbidity, and the final results of the operation show 95 per cent of successes which should be a very high recommendation.

Stem Pessary.—The stem pessary is up again for discussion after a peaceful slumber for a few years. This time RAWLS (*Am. Jour. Obst. and Gynec.*, 1921, I, 499) has studied the end results in 117 cases in which a stem pessary was used for one reason or another in the Woman's Hospital of New York and has come to fairly definite conclusions. He states that the intra-uterine stem pessary has a limited field of usefulness in gynecology. It is applicable to 51.7 per cent of cases suffering from either dysmenorrhea, sterility, amenorrhea, anteflexion of the uterus, stenosis of the cervix or congenital malformation of the uterus. As an operative measure it is applicable to 2.3 per cent of patients treated and 1.3 per cent of operations performed in a gynecological ward. From its use sequelæ other than a temporary rise of temperature occur in from 17.6 per cent to 21.8 per cent of the cases, with a permanent morbidity of from 5.8 per cent to 9.8 per cent. As a therapeutic measure for dysmenorrhea there is improvement in 77.8 per cent with relief in 61.1 per cent, and for sterility there is relief in 23.4 per cent. The intra-uterine stem pessary gives as good end-results as other operative procedures for like indications, and from its use there is less primary invalidism and no more liability to sequelæ or morbidity. The stem pessary should never be used except in carefully studied and selected cases, and then the minimum of sequelæ and morbidity with the maximum of result will be obtained, as evidenced by the careful study which the author has made.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Gonococcus Types I.—HERMANIES (*Jour. Infect. Dis.*, 1921, xxviii, 133) performed absorption tests on 85 strains of gonococci. Forty-nine of these were isolated from cases of urethritis, vulvovaginitis and ophthalmia by growing on ascites agar under the conditions of partial tension. The remaining strains were obtained from other laboratories and included the "so-called Torrey strains." It was found that the 85 strains fell into six very distinct serological types, by far the largest number of strains belonging to either type I or II. The agglutinins of a serum produced in rabbits by one type could not be absorbed by any of the strains forming the other types no matter how highly the serum was diluted and how much of the growth was used. The Torrey strains from three laboratories established themselves as members of type I, while of the ten strains received from another laboratory only four fell into this type. The remaining six formed the C race of type II. Believing that it would lead to mere assumptions the author makes no attempt at all to explain the differences in types of the Torrey strains. In a second communication (*Jour. Infect. Dis.*, 1921, xxix, 11) the same author further studied, by similar methods, the thirty-six strains forming type II in the original investigation. It was noted that these thirty-six strains grouped themselves into four fairly distinct subtypes or races. By means of a genealogical table the author shows graphically the antigen complex of the four races of type II, along with their interrelationships and their probable path of evolution. "Judging from analogy the six distinct and separate gonococci types discussed in the previous paper may have sometimes been merely races of one or two types. In the course of evolution the common connecting bond was eliminated and the races became new species. As the process of variation is still going on, and will continue as long as their living conditions are secured, there is no limit to further differentiation. A single clear-cut type may, by molecular rearrangement, acquire new antigenic characteristics and split into several races. Finally, by elimination, these may be differentiated into species."

Studies on the Pneumonic Exudate.—Having previously demonstrated in cellular material from the pneumonic lung a proteolytic enzyme active in eroding the surface of Loeffler's blood serum at P_h 7.3 to 6.7, LORD and NYE (*Jour. Exper. Med.*, 1921, xxxiv, pp. 199, 201, 207 and 211), in a series of four articles, further investigated the physical and biological properties of enzyme. It was found that the

enzyme remains active after preservation in the ice-box mixed with chloroform and toluene for eighteen months as well as at incubator temperature before and after heating to 65° C. for one hour, although it is only slightly active at room temperature and inactive after heating at 75° C. for one hour. The activity persisted when the enzyme was mixed with concentrations of sodium chloride varying from normal to 32 times normal. No dialysis of the enyzme could be demonstrated. The bile in which type I pneumococci had been dissolved caused no erosion of the blood serum. The purulent sputum obtained during life and the exudate at autopsy from the later stages of lobar pneumonia commonly eroded the Loeffler blood serum, while the cellu'ar material obtained from the pneumonic lung in an early stage of lobar pneumonia failed to erode the surface until washed with normal saline solution. Mixtures of washed pneumococcic cellular material and normal human serum failed to erode the blood serum when the amount of cellular material was less than one part of cells to approximately three parts of serum, whereas erosion did occur when the cellular material exceeded this amount in the ratio. The authors believe that these observations point to a local ferment-antiferment balance between the pneumonic exudate and the human serum *in vivo*. By washing blocks of pneumonic lung and testing the supernatant fluid with the homologous antipneumococcus serum it was found that in those cases of lobar pneumonia due to the fixed types of pneumococcus (I, II, III) a specific precipitin reaction was obtained. On the other hand specific agglutinins for the homologous pneumococcus were wanting or present only in small quantity in the pneumonic exudate. The authors conclude that the pneumonic lung contains a soluble substance inhibiting agglutination of the fixed types of pneumococci by the homologous antipneumococcus serum.

Mononuclear Phagocytes of the Lung.—PERMAR (*Jour. Med. Res.*, 1920–21, xlii, 147) gives a more detailed account of the development of the mononuclear phagocyte of the lung. The same experimental method was followed as in his first paper on these cells—that is the administration of carmine powder in salt solution intratracheally and along with this the use of a vital stain to mark the endothelial cells. Pyrrhol blue and isamine blue were the dyes used. He found that the proliferating cell first enlarged in all dimensions, without greatly altering its shape, and at this stage it had a great avidity for the dye, which at this stage appears in granules in the cytoplasm. The cell then becomes polypoid in outline and retains only a narrow attachment to the vascular lining. Then by ameboid motion the cell passes outward through this point of attachment and comes to lie outside the vessel wall, and by further migration eventually reaches the air spaces of the lung. Its passage through the alveolar lining is effected in the same way as its original exit from the capillary wall. The free cells found in the alveoli were nearly always considerably larger than those just developed and in process of migration toward the air sacs. Mitosis was very difficult to make out in the preparations studied, but there was every evidence that the process described and photographed by Mallory in his work on the skin lesions in measles is identical with what goes on in the capillaries of the lung in response to the presence of

foreign particulate material. In the latter instance, however, the process is less active than that developing in an acute infection such as measles. Nothing could be adduced to show there is any specialization of the endothelium lining the capillaries. The proliferative reaction was localized to the capillaries in the vicinity of the irritating masses (carmine) lying in the alveoli. In no instance was there observed proliferative activity on the part of endothelium lining the lymphatics of the lung. The migration and fate of the mononuclear phagocytes of the lung formed the subject of the third paper of this series (PERMAR, *Jour. Med. Res.*, 1920–21, xlii, 209). This constituted a study of what was virtually an acute experimental anthracosis in which the red granules of carmine powder replaced the familiar black granules of air-borne carbon. The vital stain was useful here, as in the preceding experiments, to enable the newly proliferated endothelial phagocytes to be identified. They could thus be traced to the air spaces, where they phagocyted the free carmine granules, and thence to the terminal lymphatics. It is of interest that the cells do not manifest the same indifference regarding their point of exit from the air spaces as they do to the point of entrance. They showed a tendency to pass into and through the somewhat heavier walls of the atria from which they have easy access to the finest pulmonary lymph channels. They were then traced along the lymphatics to the hilus, and were found in the lymph nodes here in small numbers as early as twenty-four hours after the introduction of carmine into the lung. It is worthy of note that the sudden flooding of the air sacs by the carmine powder in suspension is dealt with by the same mechanism as is the gradually insufflated carbon in anthracosis.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Making Morbidity Reports Aid the Epidemiologist.—KELLY and STEVENS (*Public Health Reports*, 1921, xxxvi, 1219), of the California State Health Department, describe the method they use for securing the greatest aid from morbidity records furnished to the health officer. There is constructed for each county a cumulative curve showing the average of each disease for each geographical unit for the preceding five years, and a similar cumulative curve is plotted for each disease each week and at once shows where the current curve deviates from the average or normal. Index maps show by different colored

pins the prevalence above the five-year average and an incidence above the preceding year; again a separate map for each disease. Spot maps for each disease show all cases for any given quarter of the year. A card record is used for comparison over larger periods and gives the precise location where control measures are necessary.

Modern Steam Laundry Processes as a Means of Destroying Vermin.—PIERCE, HUTCHINSON and MOSCOWITZ (*Public Health Reports*, 1921, xxxvi, 710) studied this subject with special reference to the utility of laundry methods for the destruction of body lice, and conclude their report with the following recommendations: "In view of the foregoing tests there is proposed as a measure in disinsection of woolens a process which not only will disinsect but also will cleanse the garment and return it to the owner in good form, without undue shrinkage. This process consists of the following measures: (1*a*) In the washer run a current of live steam for fifteen minutes, revolving the cylinder every five minutes, and discharging water of condensation every five minutes. Remove the garments and shake until almost dry. This requires only a few shakes. (1*b*) Submerge in water at 165° F. for twenty minutes, without motion, except a few revolutions every five minutes; (2) wash fifteen minutes at 131° F. in heavy suds and light load; (3) rinse three times, three minutes each, at 131° F.; (4) extract; (5) run in tumbler for fifteen minutes, at a minimum of 140° F. Live steam (1*a*) or very hot soaking (1*b*) are advised only in cases in which there is no heated tumbler (5) available, or where the garments are suspected of being contaminated with very resistant spore-bearing bacteria. In other words, the usual laundry methods for the disinfection and disinfestation are recommended because of their added value of cleansing. There can be no doubt that the ordinary processes of the laundry will kill all lice and their eggs, and probably all insect life. It is proved that woolens can be treated at a temperature which will kill lice and bacteria, without undue shrinkage—that is 131° F. Washing in heavy suds, with motion; 165° F. soaking, without motion; live steam, without motion, and occasionally removing the water of condensation; or dry tumbling of wet garments; these do not cause undue shrinkage of woolens."

Botulism and Spoiled Canned Food.—The U. S. Public Health Service (*Public Health Reports*, 1921, xxxvi 751) reviews a fatality from eating home-canned stringbeans which were canned by an approved process but which were obviously unfit for consumption. A warning is given that danger is incurred by the use of canned goods that are not entirely sound.

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All communications should be addressed to—

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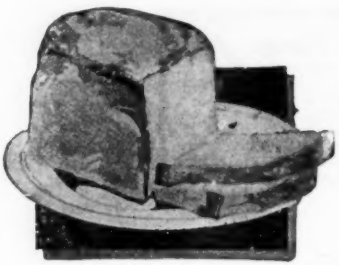

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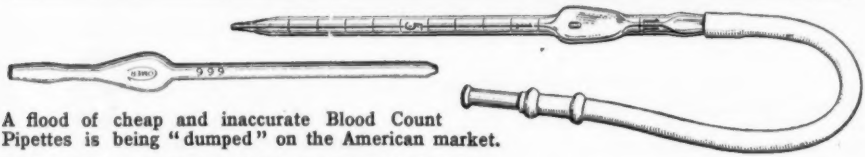

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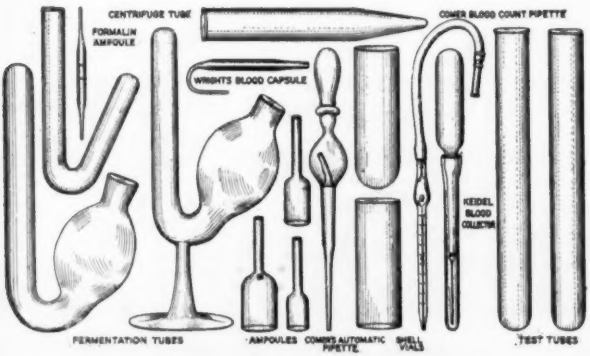

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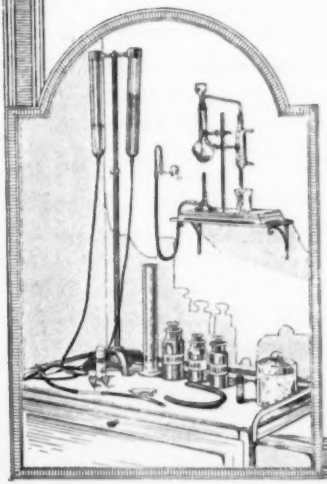

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